REPRODUCTIVE MEDICINE & ASSISTED
RM&ART
REPRODUCTIVE TECHNIQUES SERIES

The BOSTON IVF Handbook of Infertility

Third Edition

A practical guide for practitioners who care for infertile couples

Edited by
Steven R Bayer
Michael M Alper
Alan S Penzias

informa
healthcare

The Boston IVF Handbook of Infertility

REPRODUCTIVE MEDICINE AND ASSISTED REPRODUCTIVE TECHNIQUES SERIES

Series Editors

David Gardner
University of Melbourne, Australia

Jan Gerris
University Hospital Ghent, Belgium

Zeev Shoham
Kaplan Hospital, Rehovot, Israel

1. Jan Gerris, Annick Delvigne, François Olivennes *Ovarian Hyperstimulation Syndrome*, ISBN: 9781842143285
2. Alastair G Sutcliffe *Health and Welfare of ART Children*, ISBN: 9780415379304
3. Seang Lin Tan, Ri-Chen Chian, William Buckett *In Vitro Maturation of Human Oocytes*, ISBN: 9781842143322
4. Christoph Keck, Clemens Tempfer, Jen-Noel Hugues *Conservative Infertility Management*, ISBN: 9780415384513
5. Carlos Simon, Antonio Pellicer *Stem Cells in Human Reproduction*, ISBN: 9780415397773
6. Kay Elder, Jacques Cohen *Human Preimplantation Embryo Selection*, ISBN: 9780415399739
7. Michael Tucker, Juergen Liebermann *Vitrification in Assisted Reproduction*, ISBN: 9780415408820
8. John D Aplin, Asgerally T Fazleabas, Stanley R Glasser, Linda C Giudice *The Endometrium, Second Edition*, ISBN: 9780415385831
9. Adam H Balen *Infertility in Practice, Third Edition*, ISBN: 9780415450676
10. Nick Macklon, Ian Greer, Eric Steegers *Textbook of Periconceptional Medicine*, ISBN: 9780415458924
11. Carlos Simon, Antonio Pellicer *Stem Cells in Human Reproduction, Second Edition*, ISBN: 9780415471718
12. Andrea Borini, Giovanni Coticchio *Preservation of Human Oocytes,* ISBN: 9780415476799

The Boston IVF Handbook of Infertility

A Practical Guide for Practitioners who Care for Infertile Couples

Third Edition

Edited by
Steven R Bayer MD
Michael M Alper MD
Alan S Penzias MD
Boston IVF and Harvard Medical School
Boston, Massachusetts
USA

informa
healthcare
New York London

Second Edition published in 2006 by Informa UK Ltd.

This edition published in 2012 by Informa Healthcare, Telephone House, 69-77 Paul Street, London EC2A 4LQ, UK.

Simultaneously published in the USA by Informa Healthcare, 52 Vanderbilt Avenue, 7th Floor, New York, NY 10017, USA.

Informa Healthcare is a trading division of Informa UK Ltd. Registered Office: 37–41 Mortimer Street, London W1T 3JH, UK. Registered in England and Wales number 1072954.

A CIP record for this book is available from the British Library.

ISBN-13: 9781841848105
ISSN (print): 2158-0197
ISSN (online): 2158-0200

Orders may be sent to: Informa Healthcare, Sheepen Place, Colchester, Essex CO3 3LP, UK

Telephone: +44 (0)20 7017 5540
Email: CSDhealthcarebooks@informa.com
Website: http://informahealthcarebooks.com/

Library of Congress Cataloging-in-Publication Data

The Boston IVF handbook of infertility : a practical guide for practitioners who care for infertile couples / edited by Steven R. Bayer, Michael M. Alper, Alan S. Penzias. -- 3rd ed.

p. ; cm. -- (Reproductive medicine and assisted reproductive techniques series)

Handbook of infertility

Includes bibliographical references and index.

ISBN 978-1-84184-810-5 (pb : alk. paper)

I. Bayer, Steven R. II. Alper, Michael M. III. Penzias, Alan S. IV. Boston IVF. V. Title: Handbook of infertility. VI. Series: Reproductive medicine & assisted reproductive techniques series.

[DNLM: 1. Infertility--diagnosis--Handbooks. 2. Infertility--therapy--Handbooks. 3. Reproductive Techniques, Assisted--Handbooks. WP 39]

LC-classification not assigned

618.1'78--dc23

2011029661

For corporate sales please contact: CorporateBooksIHC@informa.com
For foreign rights please contact: RightsIHC@informa.com
For reprint permissions please contact: PermissionsIHC@informa.com

Typeset by MPS Limited, a Macmillan Company.
Printed and bound in the United Kingdom.

Contents

Contributors

Michael M Alper Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Steven R Bayer Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Brian M Berger Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Merle J Berger Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Alice D Domar Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Benjamin Lannon Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Stephen A Lazarou Harvard Medical School, Boston, Massachusetts, USA

Vasiliki A Moragianni Harvard Medical School, Boston, Massachusetts, USA

Khanh-Ha D Nguyen Harvard Medical School, Boston, Massachusetts, USA

Lynn Nichols Boston IVF, Boston, Massachusetts, USA

Selwyn P Oskowitz Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Karen Parlee Boston IVF, Waltham, Massachusetts, USA

Alan S Penzias Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Terry Chen Rothchild Boston IVF, Boston, Massachusetts, USA

David A Ryley Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Rita M Sneeringer Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Kim L Thornton Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Jeanie Ungerleider Boston IVF, Boston, Massachusetts, USA

Alison E Zimon Boston IVF, Harvard Medical School, Boston, Massachusetts, USA

Preface

This is the third edition of the *Handbook of Infertility* by Boston IVF, one of the most respected Assisted Reproduction and Women's Health clinics in the United States. I have had the privilege to get to know well the two senior authors, Michael Alper and Alan Penzias, over the last few years. Michael is a role model for many IVF physicians and an expert in patient care, quality management, and clinical innovation. He is an amazing speaker and writer whose folksy charm and self-deprecating humor belies a wealth of knowledge and experience in ART, both clearly evident in this book. Alan Penzias is a superb clinical researcher and teacher who brings to the book critical thinking, technological expertise, as well as his love for medical history. Together with Steven Bayer and the other physicians and scientists from Boston IVF, the authors' personalities infuse the text of this book and allow many interesting ideas to take flight. Far from the usual didactic textbook, this book by the staff of Boston IVF is easily readable and covers a wide range of subjects in ART, ranging from an introductory history of infertility and its management to the latest scientific advances in preimplantation genetic diagnosis and embryo chromosomal screening. There are unique insights into fertility quality management and excellence in patient care, two areas that the senior authors have pioneered and attempted to perfect at Boston IVF. The chapter on medical ethics is exceptional, including practical examples in the form of six case reports. These three chapters are often neglected in standard texts of infertility and reflect both the practical business management of an ART clinic as well as the sensibilities and values of the authors in dealing with patients in their daily practice. I believe this book is valuable for infertility nurses, general obstetricians/gynecologists, and infertility counselors, and a must-read for first-year fellows and for residents considering a career in reproductive endocrinology and infertility.

Robert F Casper
Professor,
Division of Reproductive Sciences, University of Toronto,
Camille Dan Family Research Chair in Translational Cell Biology
Senior Scientist,
Samuel Lunenfeld Research Institute,
Mount Sinai Hospital, Toronto,
Medical Director,
Toronto Centre for Advanced Reproductive Technology,
Toronto, Ontario, Canada

Acknowledgments

This book is dedicated to our patients, who display the utmost courage and determination in their journey to one day becoming parents.

About Boston IVF

Boston IVF was established in 1986 as one of the first freestanding IVF centers in the United States. Since its inception Boston IVF has been a leader in the cutting-edge reproductive technologies. The unique practice model and commitment to the highest quality medical care has resulted in continued growth and success of the organization. To this end, Boston IVF has established itself as one of the largest IVF centers in the United States and has been responsible for the birth of more than 30,000 babies. As a testament to its commitment to quality Boston IVF became the first IVF center in North America to become ISO-9001 certified. The strong affiliation of Boston IVF with the Beth Israel Deaconess Medical Center and the Harvard Medical School has resulted in broad-based clinical and basic science research that has helped to advance the field of infertility. Boston IVF also has maintained a strong commitment to education. There is active teaching of nurses, medical students, physicians in training and fellows. Through its commitment to quality patient care, medical research and education, Boston IVF is a recognized world leader in infertility.

Disclaimer

This handbook presents an understanding and a perspective of the current clinical and scientific advances in the field of reproductive medicine and infertility as of the date of its writing. The field of reproductive medicine and infertility is an emerging discipline and is subject to change. The information presented in this handbook should not be considered as dictating an exclusive course of treatment or procedure to be followed. Rather it is intended to be an educational aid to the physician on current information.

1 Overview of infertility

Alan S Penzias

Significant advances have been made in the field of reproductive medicine over the past several decades. The knowledge that has been gained has provided a better understanding of the science of infertility and has resulted in the development of reproductive technologies that have greatly benefited infertile couples. However, with the introduction of these new therapies, there is a realization that infertility is not a simple medical problem but there are legal, economic, moral, and ethical issues that must be addressed. This chapter provides an overview of infertility and discusses its broader impact on society today.

HISTORICAL PERSPECTIVE

Realizing the importance of reproduction, early scientists, philosophers, and others have ventured to gain an understanding of the human reproduction system and the disorders that alter its function. While most of our understanding of human reproduction has been gained over the last 50 years, this could not have been possible without the insight and knowledge from early investigation.

Infertility in the Bible

The earliest references to reproduction date back to antiquity with the biblical directive to "be fruitful, and multiply" (1). In fact, these words are used three separate times in the book of Genesis (2,3). It is no surprise therefore that fertility and procreation played a cornerstone of early life and beliefs. A woman was measured by her ability to bear children and infertility was viewed as a punishment for wrongdoing, with God being the source of fertility.

Problems with infertility beset our ancestors from the start. Sarah and Abraham were unable to conceive (4). Sarah considered the problem and asked Abraham to "go in unto my maid; it may be that I may obtain children by her" (5). Abraham honored Sarah's request and Hagar conceived. We can probably view this as the first recorded test of male infertility but in retrospect confirmed that the infertility resided with Sarah.

Ancient Greece

Hippocrates (460–380 B.C.) was one of the first authors of various medical works dealing with gynecology. Six treatises that deal with reproduction were attributed to him. The diagnosis of infertility was based on the concept of free passage or continuity of the external genitalia and the vagina with the rest of the body. In the Aphorisms of Hippocrates, he wrote "If a woman do not conceive, and wish to ascertain whether she can conceive, having wrapped her up in blankets, fumigate below, and if it appear that the scent passes through the body to the nostrils and mouth, know that of herself she is not unfruitful" (6). In the same treatise, Hippocrates speculated on the conditions needed to foster pregnancy. "Women who have the uterus cold and dense do not conceive; and those also who have the uterus humid, do not conceive, for the semen is extinguished, and in women whose uterus is very dry, and very hot, the semen is lost from the want of food; but women whose uterus is in an intermediate state between these temperaments prove fertile" (6).

Aristotle of Stagira (384–322 B.C.) who was one of the greatest Greek philosophers of his time was also one of the greatest zoologists and naturalists of antiquity. Although not a physician, he discussed many issues relating to reproduction in his thesis *The Generation of Animals*. Aristotle gave to medicine certain fundamentals such as comparative anatomy and embryology. A common ancient method of interfering with male fertility was castration. Aristotle knew that castration makes a male infertile despite his belief that the testes are only weights holding down the spermatic passages and not the source of the seed. "For the testes are no part of the ducts but are only attached to them, as women fasten stones to the loom when weaving" (7). He was probably misled by his observation that a recently castrated bull

succeeded in impregnating a cow "a bull mounting immediately after castration has caused conception in the cow because the ducts had not yet been drawn up" (7).

The Renaissance

Andreas Vesalius (1514–1564), a Belgian physician and anatomist, published his revolutionary book *De Humani Corporis Fabrica* (On the Structure of the Human Body) in 1543. Vesalius contributed to an accurate description of the entire female genital system including ligaments, tubes, and blood supply. He was the first to use the terms "pelvis" and "decidua." He also was the first to describe the ovarian follicle.

Gabrielle Fallopio (1523–1562) of Modena was a student of Vesalius. He described the oviducts and wrote further on the morphology of the ovaries. His name has been permanently connected with the oviduct or fallopian tube. He also named the clitoris, the vagina, and the placenta.

Lazzaro Spallanzani (1729–1799), though not a physician, made enormous contributions to our understanding of fertility. In his monograph, *Fecondazione Artificiale*, he showed that conception was achieved as a result of contact between eggs and sperm. He succeeded in fertilizing frog eggs by placing them in the immediate contact with the secretions expressed from the testicles of the male frog. He also performed some of the first successful artificial insemination experiments on lower animals and on a dog (8).

Modern Era

Marion Sims (1813–1883) is considered the father of American gynecology. Among his numerous contributions, Sims played an important role in establishing the role of cervical secretions in affecting sperm survival in the genital tract. On the basis of Sims work, Max Huhner (1873–1947) in his 1913 book, *Sterility in the Male and Female and Its Treatment*, introduced the Sims–Huhner test (later termed the postcoital test).

I.C. Rubin introduced the first clinical test to determine tubal patency. Initially, he started by using a radioactive material but realized that this approach had its limitations. He then turned to tubal insufflation using oxygen in 1920. This was later changed to carbon dioxide as it was reabsorbed more easily, caused less discomfort, and avoided the danger of embolism. In the test, the insufflation is usually carried out at a gas pressure of less than 120 mmHg. The manometer reading decreases to 100 or less if the tubes are clear; if between 120 and 130, there is probably partial stricture; if it rises to 200 and above, it is suggestive that the tubes are obstructed (9). This test is no longer performed as there are many more accurate tests of tubal patency available.

In 1935, Stein and Levanthal described a series of patients with amenorrhea, hirsutism, and obesity. They named the condition the Stein–Levanthal syndrome (later termed polycystic ovarian syndrome). They noted that several of these women started to menstruate after they underwent an ovarian biopsy. This led to the development of the wedge resection as a treatment for this condition which proved to be quite effective in the restoration of menstrual function. To this day, we still do not have an understanding as to why an ovarian wedge resection or the modern day ovarian drilling procedure is effective.

1950s—The Development of the Radioimmunoassay

In the 1950s, the radioimmunoassay (RIA) was developed by Solomon Aaron Berson and Rosalyn Sussman Yalow. The RIA allowed the detection and measurement of steroid and peptide hormones that are present in the serum and urine in very low concentrations. As a result of this monumental work, Yalow received the Nobel Prize in physiology in 1977. The introduction of RIA was pivotal and developed the foundation to modern day endocrinology. The information gained helped us to understand the steroid pathways in endocrine organs and also helped with the diagnosis and characterization of endocrine disorders. The RIA also provided an important tool in monitoring the patient undergoing ovulation induction.

1960s—The Introduction of Fertility Medications

Clomiphene citrate (CC) was an oral medication introduced in 1962. It was the first medical therapy developed to correct ovulatory dysfunction secondary to anovulation. To this day, it continues to be the most commonly prescribed medication for the infertile female.

In the 1960s, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were extracted from the urine of menopausal women, which gave rise to the development of an injectable medication called human menopausal gonadotropins. This medication was used for ovulatory dysfunction that was refractory to CC. It was a much stronger agent and required closer monitoring of serum estradiol levels that could now be measured by RIA. In 1962, Dr Bruno Lunenfeld in Israel reported the first pregnancy achieved with the use of human menopausal gonadotropins.

1980s—Reproductive Surgery

During the 1980s, there was an emphasis on reproductive surgery to correct tubal/peritoneal factors that were causing infertility. Laparoscopy was becoming increasingly popular and evolved into a routine part of the infertility evaluation. Laparoscopy was first introduced in the United States in 1911 by Bertram Bernheim at The John Hopkins Hospital. It was not until the introduction of the automatic insufflator in 1960 and the development of a fiber optic light source, did the procedure become practical. Initially, laparoscopy was only a diagnostic tool and the surgeon would have to resort to a laparotomy to correct altered pelvic anatomy. In the ensuing years, with the advent of laparoscopic instrumentation, operative laparoscopy was born, which allowed the surgeon to not only diagnose but treat most abnormalities that were encountered. However, in the 1990s, rising in vitro fertilization (IVF) success rates soon surpassed the success rates resulting from corrective surgery. Presently, there are fewer indications to resort to surgery.

1990s—The IVF Revolution

On July 25, 1978, Louise Joy Brown, the world's first successful "test tube" baby, was born in Great Britain. This marvelous achievement earned Robert Edwards the 2010 Nobel Prize in Physiology or Medicine. The first IVF success was a culmination of decades of work. In 1944, along with Harvard scientist Miriam F. Menkin, John Rock fertilized the first human egg in a test tube. On February 6, 1944, they produced the first laboratory-fertilized, two-cell human egg (10).

Author Martin Hutchinson summarized the chronology of IVF technology when he wrote:

> The idea of in vitro fertilisation had first been put forward as early as the 1930s, but it was not until the 1950s that anyone managed to fertilise a mammal egg in a test tube. Rabbits were one thing, but, as scientists were finding out, the secrets of the human reproductive system proved to be hard-won indeed. Professor Edwards said: "By 1965 I'd been trying to mature human eggs for the past five years." There was nobody racing against us—nobody had figured any of the ideas of this concept. It took further years of effort to produce a magical figure—37 hours—the length of time it took for a human egg to become ready for fertilisation after a particular point in a woman's cycle (11).

The establishment of the first IVF pregnancy was truly amazing and the initial experience was detailed in a publication by Edwards et al. (12). The initial cycles involved women who were followed during their natural cycle. The LH surge was identified with three hourly LH determinations and the laparoscopic egg retrieval was scheduled accordingly. Over 30 cycles were initiated before a success was achieved which led to the birth of Louise Brown. Since the inception of IVF, many modifications have been instituted in every step of the treatment which has resulted in increased success. Following this first success, IVF programs were established all throughout the world. Presently, more than 600,000 IVF cycles are performed by 1400 clinics worldwide annually and it has been estimated that more than 3,000,000 children have been born through this technique (13,14). Today, advances in IVF technology enable conception and childbirth in couples with conditions that were previously thought to be uncorrectable. Direct aspiration of sperm from the testes; use of gestational carriers for women born without a uterus; and transplantation of frozen ovarian tissue were beyond anyone's wildest imagination in 1978. Further advances in the field of genetics and the ability to biopsy the embryo in the laboratory have created new opportunities for couples who are carriers of genetic conditions.

THE DEFINITION OF INFERTILITY

There has been considerable debate about an acceptable definition of infertility (15). First, there is confusion about the use of the word itself—"infertility" which upon translation means "not fertile" and therefore would be synonymous with sterility. While it is true that all women who are sterile would be considered infertile, the contrary is not true—not all women who are infertile are sterile. Therefore, many women would be better categorized as being "subfertile" instead of infertile. Despite these shortcomings, the all-inclusive term "infertility" is here to stay and there is little that can be done to change it.

The most succinct definition of infertility has been published and recently updated by the American Society for Reproductive Medicine (16).

> Infertility is a disease,[a] defined by the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.

A deficiency of this definition is that there is a lack of clarity as to what is meant by "regular unprotected intercourse." The time threshold of 12 months that is needed to substantiate the diagnosis is purely arbitrary. While the financiers of health care services have every reason to adhere to this definition, there is reason for health care providers to have a different perspective. Of those pregnancies that do occur, 78% to 85% are achieved in the first six months of trying. With this in mind, one could argue that an evaluation is warranted if the couple has failed to achieve a pregnancy after six months of trying. Other reasons to move up the time of the evaluation is when the woman is over the age of 35 or when there is a known or suspected cause of infertility (i.e., anovulation, a known tubal factor, endometriosis, etc.).

EPIDEMIOLOGY

Infertility continues to be a prevalent problem in our society today. Over the past few years, the many issues surrounding infertility have become popular topics in the lay press. This has resulted in an increased awareness of infertility, but has also given the impression that we are amidst an epidemic of this problem. The National Survey of Family Growth performed by the National Center for Health Statistics has provided insight into the prevalence of infertility in the United States. This survey has been performed several times since 1965 with the most recent survey of over 7000 women being performed in 2002 and the results being published in 2005 (17). The results of the survey are as follows[b]:

- 11.3% of married women, or approximately 2.1 million women, were infertile.
- The rate of infertility was correlated with age
  - 15–29 years: 7.2%
  - 30–34 years: 10.9%
  - 35–39 years: 10.5%
  - 40–44 years: 20.3%
- The rate of infertility is impacted on by parity (Fig. 1.1).
- The overall rate of infertility in 2002 was 11.3% of all women. The rate of infertility has decreased progressively. In the 1965, 1982, 1988, and 1995 surveys, it was 13.3%, 13.9%, 13.7%, and 12.0%[b], respectively (Fig. 1.2) (18).
- 35% of infertile women presented for medical help within the previous year.
- The incidence of infertility was influenced by race. The incidence in the Caucasian, Hispanic-American, and African-American populations was 10.8%, 11.7%, and 20.6%, respectively.

[a] Disease is "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown." (From *Dorland's Illustrated Medical Dictionary, 31st edition*, 2007:535.)

[b] Women who were surgically sterile were not included in the final calculation.

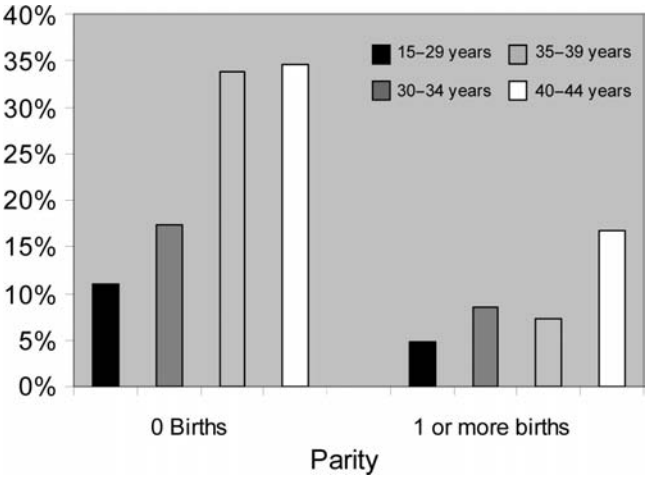

Figure 1.1 Percentage of married women 15 to 44 years of age with 12 months infertility, by parity and age: United States, 2002. Note: The calculation of percentage of infertility in age groups did not include women who had undergone a sterilization procedure. *Source*: Data obtained from Ref. 17.

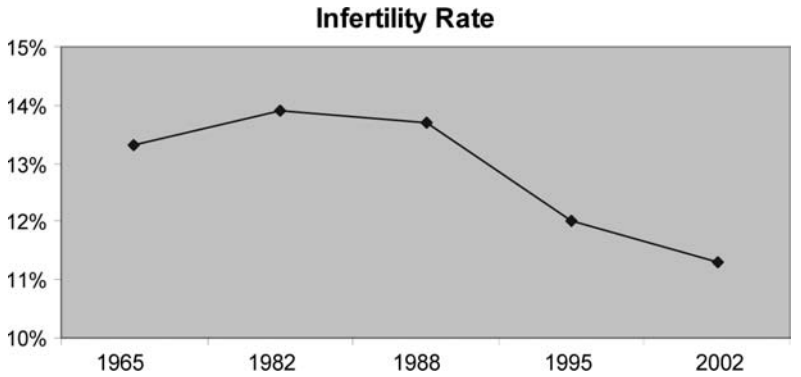

Figure 1.2 Percentage of married women 15 to 44 years of age with 12 months infertility, from 1965 to 2002. The rate of infertility has decreased over time. From 1982 to 2002, the rate has dropped almost 20% (13.9–11.3%). Note: Those women who were surgically sterile were not included in the final calculation. *Source*: Data obtained from Refs. 17 and 18.

Infertility continues to be a persistent problem in the United States but it has implications worldwide as well. The World Health Organization has estimated that infertility affects 50 to 80 million women worldwide, and this may be an underestimate (19). In developing countries, the incidence of infertility has been estimated to be as high as 50% (20). One reason for the higher rate of infertility in developing countries is reduced access to medical treatments including antibiotics to reduce the transmission and consequences of sexually transmitted diseases. The ramifications of infertility in these populations are far reaching. Many societies depend on their offspring for survival. In addition, the inability to bear children for some cultures results in a social stigma that can result in a loss of social status and violence. The challenge is how to provide infertility services in a cost-effective and accessible way to all women. However, many countries are less apt to provide infertility services since their ultimate goal may be to control population growth.

Economics

The total expenditure on infertility services in the United States is estimated to be $2 to $3 billion per year. While this initially appears to be a significant amount of health care dollars, it is a

fraction of the total money expended on health care in the United States, which in 2009 was estimated to be close to $2.5 trillion. Many countries provide infertility services within their national health care system. However, insurance coverage for infertility treatment in the United States is left up to employers and insurance plans which can be influenced by state insurance mandates. Most American women do not have insurance coverage for this medical problem.

How do we achieve more wide-scale coverage for infertility services? First, the stigma of infertility must be overcome. Society does not view infertility as a medical problem and considers the treatment to be elective, likened to plastic surgery. It is paradoxical that as a society there are no qualms about paying for the medical expenses for individuals who have been irresponsible and caused themselves harm with smoking or alcohol abuse. In contrast, for the majority of infertile couples, irresponsible behavior is not a cause of their plight. The solution is to establish infertility as a medical diagnosis. Some states have already done this to some degree but we have to get other states to follow suit. The federal government has also taken a stand—in 1998, the Supreme Court ruled that reproduction is a major life activity under the American with Disabilities Act.

The other misconception that must be overcome is that the costs of infertility treatment are a drain on the health care system. This is in part fueled by the costly price tag of some of the treatments. For instance, the cost of an IVF cycle can range from $5000 to $15,000. However, since those seeking IVF treatment are only a small percentage of the population, the expense of treatment has minimal impact on society, namely the insurance companies. In a previous publication, Griffin and Panak reported on the impact of infertility expenditures on Health Maintenance Organizations (HMOs) in Massachusetts where infertility coverage is a mandated benefit (21). Infertility expenditures amounted to only 0.41% of total expenditures by the HMOs. This translates into an additional cost of $1.71 to each member per month. While this is an added minimal expense, there may be substantial savings to the insurance company to cover IVF-related services since high-order multiple pregnancies that are extremely costly are more likely to occur with other treatments. The truth is that infertility coverage is an inexpensive benefit for the insurance companies to bear. Presently, 14 states have infertility mandates in place but it has been 10 years since the passage of the last state law (New Jersey, 2001). Unfortunately, as a society we are dealing with escalating health care costs and individual states and insurance companies may be reluctant in expanding services to the infertile couple.

The consequences of fertility treatments, namely multiple pregnancies, also pose a cost to society. The utilization of fertility treatments including ovulation induction drugs (with and without inseminations) and IVF has resulted in a significant increase in the number of multiple pregnancies. There is special concern over high-order multiple pregnancies (triplets and more) that have a higher rate of complications. The rate of high-order multiple pregnancies quadrupled from 1980 to 1997 (37 vs. 174 per 100,000 live born infants) (22). This is no doubt the result of an increased number of patients seeking infertility treatments. While IVF success rates have continued to increase, most couples opt to transfer multiple embryos to increase their chance of success. This is more likely to occur if the couple is paying out of pocket for the treatment which will limit the number of cycles they can afford. A previous report demonstrated that the multiple pregnancy rates were lower in states that had laws in place to provide IVF coverage (38% vs. 43%) (23).

The impact of a high-order multiple pregnancies is immense. There is an increased risk of maternal and fetal complications, with the most significant complication being prematurity and its attended consequences. Babies born from a triplet pregnancy have a 20% chance of a major handicap, 17-fold increase in cerebral palsy, and 20-fold increase in death during the first year after birth (as compared to a singleton pregnancy) (24). There is a substantial cost to care for these premature infants; the approximate cost estimates in 2010 U.S. dollars for a twin, triplet, and quadruplet pregnancy are $90,000, $260,000, and $400,000, respectively (25). In the 1990s, there was a concerted effort from the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine to develop guidelines to help reduce the number of embryos transferred (26,27). These efforts have been effective and since 1997 there has been a plateau in the number of high-order multiple pregnancies (Fig. 1.3). In addition, the continued progress in the field has produced higher implantation rates, which

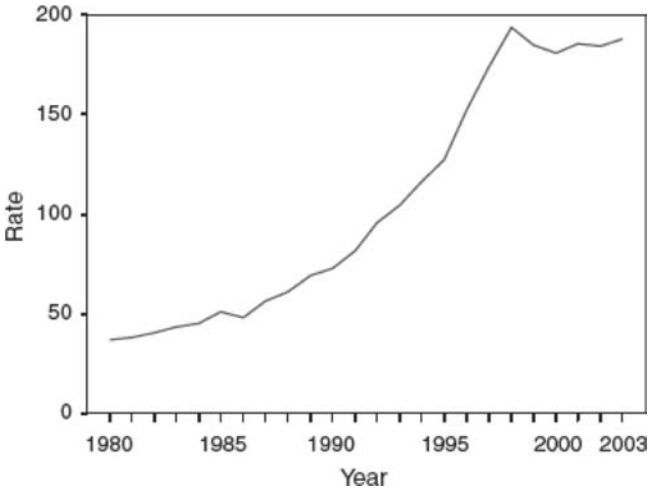

Figure 1.3 Rate per 100,000 live births of triplet and other higher-order multiple births in the United States from 1980 to 2003. *Source*: From Ref. 28.

also has provided a further impetus to reduce the number of embryos transferred without impacting on pregnancy rates (29). With the continued improvement in outcomes, there is not now consideration to transferring a single embryo in selected cases.

Ethics

The right to procreate is an undeniable human right. This is not refuted but the major question in society today is how far are we willing to go with technology to produce an offspring? The surge of ethical issues no doubt has resulted following the advent of IVF and IVF-related procedures. The first IVF success in 1978 was the result of historic work by Drs Patrick Steptoe and Robert Edwards that spanned almost an entire decade. When it became apparent where they were heading with their research, two notable ethicists, Leon Kass and Paul Ramsey, voiced vehement objections over the direction and ultimate goal of their work (30,31). The ethical concerns primarily focused on the potential harm to offspring that would be born as a result of IVF. The momentum of their work progressed and ultimately resulted in the birth of Louise Brown in 1978. Soon after, hundreds of IVF centers have opened up in the United States and abroad. It has been estimated that 3 million babies have been born as a result of IVF technology. There have been multiple studies reporting on the babies born from IVF and there is no conclusive evidence that IVF increases the risk of birth defects. Therefore, as we look back, the previous ethical concerns about IVF were unfounded. However, IVF was only the beginning and has been a platform for other treatments including egg donation, gestational surrogacy, and preimplantation diagnosis (PGD), which has resulted in new ethical dilemmas.

There are ongoing ethical concerns about third party reproduction arrangements, the most common of which is egg donation. The majority of egg donation arrangements are with anonymous donors. While there may be an element of altruism, the main reason why women donate eggs is financial. Egg donors need to be paid for their services but how much is too much? Advertisements have appeared in college newspapers recruiting prospective donors with a certain level of intelligence, physical characteristics, and athletic ability with price tags up to $50,000 to $100,000? These high prices devalue the whole process and likens egg donation to the trading of a commodity. Most in field regard these practices as unacceptable. Furthermore, the financial enticement significantly weakens the informed consent process of the egg donor. In addition, it may affect the donor in being forthright in providing important aspects of her medical and family history that could disqualify her. The American Society for Reproductive Medicine has addressed this concern and provided some guidelines for what is considered a

fair payment to egg donors. While these guidelines are quite reasonable, the physician many times is not privy to the financial dealings between the recipient couple and the egg donor.

PGD is another development of IVF and is now being offered by many IVF centers. The first case of PGD was performed on human embryos in 1992 to screen the embryos for cystic fibrosis (32). There are now many genetic conditions that can be tested for by using PGD. There is no disagreement that PGD should be performed to prevent the transmission of a serious disease, but what about its performance for other reasons? Presently, we can assess embryos for their chromosomal makeup which may be beneficial for the woman with repeated miscarriages, the older woman undergoing IVF, or one who is a carrier of a balanced translocation. What do we do with the *fertile* couple who requests PGD for the purposes of sex selection? This brings up several ethical concerns, and many IVF centers have taken the stand that they will not perform PGD for this purpose. With the mapping of human genome, the fear is that one day a fertile couple presents for IVF and requests that only embryos with genes for intelligence, athleticism, and blond hair and blue eyes be replaced. The possibilities are daunting.

Other ethical questions surround IVF when it is not used for reproductive purposes. We have the ability to support the development of the human embryo in the laboratory to the blastocyst stage. At this stage of development, differentiation of the embryo has occurred into the inner cell mass and trophectoderm. Within the inner cell mass are totipotent cells that have the ability to develop into any cell type within the body. In 1998, the first embryonic cell line was developed following the isolation of cells from a blastocyst. The possibilities are immense and these cell lines are now being used to get a better understanding of disease processes and hopefully this will lead to development of new therapies and possible cures. Where do these embryos come from? Many have voiced concerns about paying egg donor to create these embryos for research purposes only. Another source is spare embryos that are already frozen. It is estimated that over 200,000 cryopreserved human embryos are stored in IVF programs throughout the United States. The fate of most of these embryos is uncertain but most will not be used by the couple for reproductive purposes. In 2000, Boston IVF was approached by scientists at Harvard University about developing human embryonic stem cell lines from blastocysts. The goal of the work was to better understand the pathogenesis and develop new therapies for type I diabetes. The research is privately funded because at that time federal sanctions prohibited the National Institute of Health (NIH) from funding this type of research. The research was approved by the Institutional Review Board (IRB). Patients who made a decision to discard their embryos were contacted to see if they would be interested in donating them for this research. The response was overwhelming and many couples donated their spare embryos for the research. Several stem cell lines have been developed and the research is ongoing. There is ongoing debate in society as to when life begins and whether the use of embryos in this fashion breeches ethical boundaries.

The manipulation of human gametes in the laboratory as part of IVF has also created another possibility which is cloning. Cloning is not a new concept. In the 1950s, scientists used this technology to successfully clone salamanders and frogs. In the years that followed, the technique was attempted with mammals but was fraught with failure and it was concluded at that time that mammalian cells were too specialized to clone. However, progress in the area continued and in 1996 Campbell et al. successfully cloned the first mammal, an adult sheep (33). To accomplish this feat, these researchers took mammary gland cells from an adult sheep and placed them in a culture solution with only minimal nutrients, essentially starving the cells and causing shutdown of major genetic activity. With an electrical current they were able to fuse a mammary cell with an enucleated egg cell which was then transferred into a host uterus. The initial attempts were met with failure and some abnormal lambs were born and died. Finally, after 300 attempts, they were successful and "Dolly" was born. Other mammals have been cloned since including cows, mice, pigs, and horses. There are many benefits to cloning. In the agriculture industry, cloning animals allows the creation of better livestock for food production. Cloning animals that have been genetically altered allows the production of human proteins and organs that are suitable for transplantation. Cloning humans may also be beneficial in fighting disease. For instance, it may be possible to take normal heart cells from an individual afflicted with heart disease, clone the normal cells, and then inject them back into

the diseased heart. This may also prove successful in treating those with spinal cord injuries, leukemia, kidney disease, and other disorders. However, there is concern that human cloning may be used for reproductive purposes. There are many ethical concerns about human cloning for this purpose and many find simply appalling. Over the past several years, plans have been announced to proceed with human cloning for reproductive purposes. In response, many countries throughout the world have placed a ban on this research. To date, there is no federal legislation in the United States placing a ban on the practice, but many states have enacted their own legislation.

REGULATION

There has been a call for the government to step in and regulate the infertility field. One piece of regulation that has been enacted in the United States is the Fertility Clinic Success Rate and Certification Act of 1992. The objective behind the bill and ultimately the law is to make IVF units accountable for their statistics and make the statistics available to the consumers. It is now mandatory for all IVF units to submit their statistics to the Center for Disease Control (CDC) on a yearly basis. The impetus behind this legislation is that these published statistics will allow consumers to compare "quality" between centers and help them with their selection. Unfortunately, it does everything but accomplish this goal. By the time the statistics are published, they are two to three years old and do not necessarily reflect the practices of any clinic in the present time. The outcomes are impacted on by any clinic's inclusion and exclusion criteria used for patient selection. For instance, a center can increase its success rate by moving patients more quickly to IVF or discouraging those with a lower than average success rate from undergoing the treatment. In addition, clinics are encouraged to transfer more embryos to increase their rate, but of course this increases the chance of a multiple pregnancy. Furthermore, some IVF centers are misusing their statistics for self-promotion and advertising. Quite amazingly, statistics are even being used by insurance companies to determine which centers they will contract with. This is a very poor practice and induces physician practices that are not in the patient or insurance company's interests. Unfortunately, the law is here to stay. There has been a move for states to regulate IVF units especially after the birth of the octoplets in California in 2009. Many have previously enacted legislation dealing with embryo research and cloning and there is reason to believe that they will broaden their regulation in other areas of the specialty. Regulation is common abroad as well. Many countries limit the number of embryos that are transferred and some have banned egg donation, sperm donation, and gestational surrogacy.

CONCLUSION

With the advent of the reproductive technologies, infertility has become a complex medical problem with legal, moral, ethical, and financial implications that relate to the infertile couple and society at large. We have come so far and who knows where we will be 20 to 30 years from now.

REFERENCES

1. Genesis 1:28.
2. Genesis 9:1.
3. Genesis 9:7.
4. Genesis 16:1.
5. Genesis 16:2.
6. From the Aphorisms of Hippocrates. Adams F, trans. Available at: http://classics.mit.edu/Hippocrates/aphorisms.html. Retrieved May 5, 2006.
7. Aristotle. On the Generation of Animals. Platt A, trans. Available at: http://ebooks.adelaide.edu.au/a/aristotle/generation/complete.html. Retrieved May 5, 2006.
8. Lazzaro Spallanzani. Available at: http://www.whonamedit.com/doctor.cfm/2234.html. Retrieved May 5, 2006.
9. Rubin's Test. Encyclopedia Britannica. Available at: http://wwwa.britannica.com/eb/article-9064325. Retrieved May 5, 2006.
10. Today in Science. Available at: http://www.todayinsci.com/cgi-bin/indexpage.pl?http://www.todayinsci.com/2/2_06.htm. Retrieved May 5, 2006.

11. Hutchinson M. Edwards: the IVF pioneer. BBC News Online Staff. Available at: http://news.bbc.co.uk/2/hi/health/3093429.stm. Retrieved May 5, 2006.
12. Edwards RG, Steptoe PC, Purdy JM. Establishing full-term human pregnancies using cleaving embryos grown in vitro. Br J Obstet Gynaecol 1980; 87:737–756.
13. de Mouzon J, Goossens V, Bhattacharya S, et al., and The European IVF-monitoring (EIM) Consortium. Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE. Hum Reprod 2010; 25:1851–1862 [Epub Jun 22, 2010].
14. Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Atlanta: U.S. Department of Health and Human Services, 2010.
15. Habbema JDF, Collins, J, Leridon H, et al. Towards less confusing terminology in reproductive medicine: a proposal. Hum Reprod 2004; 19:1497–1501.
16. Definition of infertility and recurrent pregnancy loss. The Practice Committee of the American Society for Reproductive Medicine. The American Society for Reproductive Medicine, Birmingham, Alabama. Fertil Steril 2008; 90:S60.
17. Fertility, family planning and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. Available at: http://www.cdc.gov/nchs/nsfg.htm.
18. Mosher WD, Pratt WF. Fecundity and infertility in the United States, 1965–98. Hyattsville, MD: National Center for Health Statistics. Advance Data from Vital and Health Statistics, No. 192. December 4, 1990. 12 pp. (PHS) 91-1250. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/ad/200-151/200-151.htm.
19. World Health Organization. Infertility: a tabulation of available data on prevalence of primary and secondary infertility. Geneva, WHO, Programme on Maternal and Child Health and Family Planning, Division of Family Health, 1991.
20. Cates W, Farley TM, Rowe PJ. Worldwide patterns of infertility: is Africa different? Lancet 1985; 2:596–598.
21. Griffin M, Panak WF. The economic cost of infertility-related services: an examination of the Massachusetts infertility insurance mandate. Fertil Steril 1998; 70:22–29.
22. Martin JA, Park MM. Trends in twin and triplet births: 1980–97. National Vital Statistics Report. Vol 47, No. 24. Hyattsville, Maryland: US Department of Health and Human Services, CDC, National Center for Health Statistics, 1999.
23. Reynolds MA, Schieve LA, Jeng G, et al. Does insurance coverage decrease the risk for multiple births associated with assisted reproductive technology? Fertil Steril 2003; 89:16–23.
24. American College of Obstetricians and Gynecologists. Multiple gestation: complicated twin, triplet and high order multifetal pregnancy. Clinical Management Guideline for Obstetricians and Gynecologists, No. 56, October 2004.
25. ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000; 15:1856–1864.
26. American Society for Reproductive Medicine. Guidelines on number of embryos transferred. A Practice Committee Report—A Committee Opinion (Revised). American Society for Reproductive Medicine, 1999.
27. American College of Obstetricians and Gynecologists. Nonselective embryo reduction: ethical guidance for the obstetrician–gynecologist. ACOG Committee Opinion 215. Washington: American College of Obstetricians and Gynecologists, 1999.
28. QuickStats: Rate of Triplet and Other Higher-Order Multiple Births—United States, 1980–2003. MMWR 2005; 54(41):1058. The reference can also be viewed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5441a10.htm.
29. Tepleton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. N Engl J Med 1998; 339(9):573–577.
30. Kass LR. Babies by means of in vitro fertilization: unethical experiments on the unborn? N Engl J Med 1971; 285(21):1174–1179.
31. Ramsey P. Manufacturing our offspring: weighting the risks. Hastings Cent Rep 1978; 8(5):7–9.
32. Handyside AH, Lesko JG, Tarin JJ, et al. Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis. N Engl J Med 1992; 327:905–909.
33. Campbell KHS, McWhir J, Ritchie WA, et al. Sheep cloned by nuclear transfer from a cultured cell line. Nature 1996; 380:64–66.

2 Factors affecting fertility

Steven R Bayer

There are many known and unknown factors that impact on the human reproductive system. Of the known factors, some can be altered thereby increasing the chances of pregnancy, while others cannot. Some of the more important factors that have been studied are discussed below.

MATERNAL AGE

The single most important factor that influences a couple's chance of conceiving either naturally or following treatment is the woman's age. This has become more of an issue since many women are delaying their childbearing which has been a trend noted over the last several decades (1). In the United States, from 1979 to 2005, the average age of the first-time mothers has increased by 3.6 years from 21.4 to 25 years. First-time mothers who were 35 years or older increased by eightfold during this same period from 1% to 8% of all births. This trend is not just occurring in the United States but has been reported in other developed countries as well. The reasons for the delay in childbearing are many, some being women have more contraceptive agents to choose from, are pursuing higher education and careers, and are marrying later. A major problem is that many women are unaware of the age factor and wait until it is too late to pursue a pregnancy. The media has not helped with the reporting of celebrities, many in their late forties and even fifties, who have achieved pregnancy "on their own" when, in fact, these pregnancies were achieved with egg donation.

A woman's fertility generally begins to decline after the age of 24, and there is an acceleration of the decline after the age of 37 (Fig. 2.1). The frequency of intercourse decreases with age but this does not solely account for the decline. In the past, there were two theories proposed to explain the decreased fertility including an age-related uterine dysfunction and reduced egg quality. There was support for the former theory in the animal model. However, the overwhelming success of egg donation in older women has established that the age-related decrease in fertility is the result of declining egg quality.

In one respect, a woman's future fertility is in progressive decline since birth when one considers the contingent of oocytes that reside in the ovaries. Every female is endowed with the highest number of oocytes (6–7 million) in utero at 20 weeks of gestation. The eggs are present in the primordial follicles and arrested in prophase of meiosis I. From this time, forward atresia sets in and the number of oocytes is reduced to 2 million at birth and 600,000 to 700,000 at puberty. At age 37, a woman has approximately 25,000 eggs—just over 1% of the eggs that she was born with. There is data that suggests that the process of atresia is accelerated after the age of 37 (3). While there is evidence in the mouse model that oocytes postnatally can undergo mitosis and be replenished, there is no evidence that this occurs in the human (4). Up until the time of menopause, follicular development is a continuum. The only chance that any follicle will progress to ovulation is that it must be at a critical stage of maturation and rescued by rising follicle-stimulating hormone (FSH) levels that only occur for a short period of time during the early follicular phase.

In addition to the reduced number of eggs that occur with aging, there is reduced quality of the eggs as well. With aging, there is a greater chance that the egg released at ovulation has an abnormal chromosomal contingent that results from faulty meiosis. The actual cause of the aneuploidy is poorly understood but could be the result of dysfunction of the mitotic spindles and/or a loss of adhesion between sister chromosomes that would interfere with their alignment during meiosis. These chromosomal imbalances can prevent normal fertilization and/or halt early embryonic development. Chromosomal abnormalities explain between 70% and 80% of first-trimester losses. Studies performed on embryos resulting from in vitro fertilization (IVF) have confirmed an increased incidence of aneuploidy in eggs obtained from older women (5). The incidence of aneuploidy in women over the age of 40 is >60%. The increased chance of chromosomal errors with advanced maternal age is further supported by

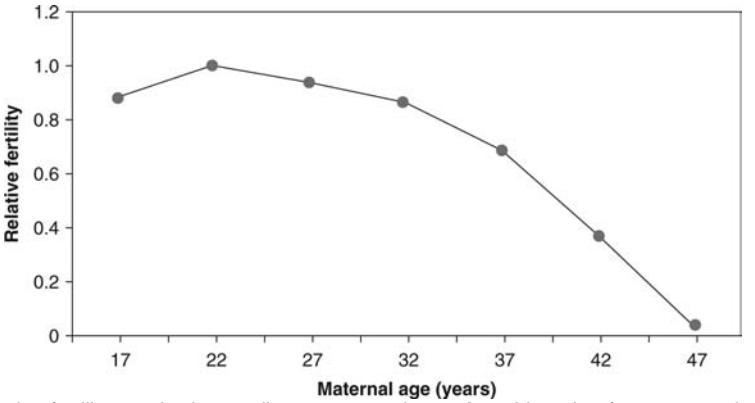

Figure 2.1 Relative fertility graphed according to maternal age. An odds ratio of 1.0 was assigned to the 20 to 24 year age group that has the highest fertility rate. *Source*: Data modified from Ref. 2.

the increased rate of spontaneous abortions and chromosomal anomalies in babies born to older women (6).

PATERNAL AGE

Like their female counterparts, males are also delaying their time in becoming a father. The impact of paternal age on fertility has been a subject of continued debate and the topic of two reviews (7,8). As do their female counterparts, men experience decreased gonadal function with advancing age. Testosterone production begins to decrease around the age of 40 (9). A male at age 75 has about half of the circulating free testosterone as a male does in his twenties (10). Semen parameters also change with aging—there is a decrease in the semen volume, motility, and normal morphology. In review of prior studies, it has been suggested that the aging male has reduced fertility that begins in the late thirties and early forties. Despite these changes, the reduction in a man's fertility is subtle and in some men may be insignificant. While a woman's fertility drops precipitously in the fourth decade, men can maintain their fertility into their sixties and even later. A significant number of pregnancies are fathered by men over the age of 50 in Japan and Germany (Fig. 2.2). The oldest father on record is 94 years of age (11). Further, a recent review by Dain et al. of 10 studies that examined the impact of paternal age on assisted reproductive technology (ART) outcome concluded that there was insufficient data to suggest that paternal age altered the outcome of IVF treatment (12).

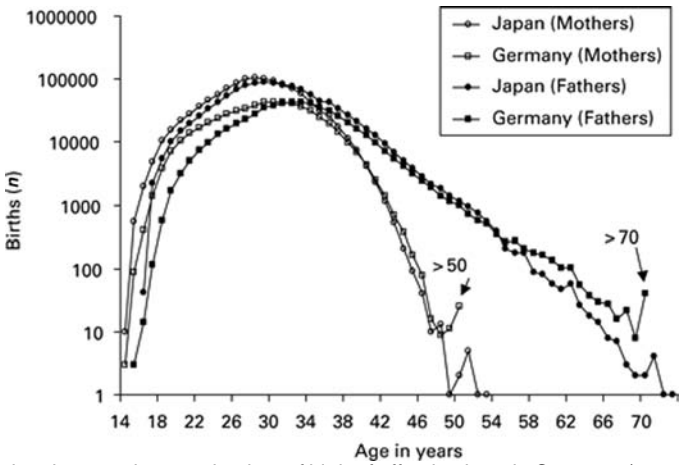

Figure 2.2 Maternal and paternal age at the time of birth of offspring born in Germany (2001; $n = 550{,}659$) and in Japan (2002; $n = 1{,}135{,}222$). *Source*: From Ref. 8. (Reprinted from Kühnert B, Nieschlag E. Reproductive functions of the ageing male. Human Reproduction Update 2004 10(4):327–339. ©European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/Human Reproduction.)

The rate of aneuploidy in oocytes increases with a woman's age and is the cause of most pregnancy losses. Aneuploidy or disomy in sperm may explain some pregnancy losses. The rate of aneuploidy in sperm is 2%, and there is no evidence to support an increased rate of aneuploidy involving autosomes in men with advanced age (13). However, there is data to support that with advanced paternal age, there is an increased risk of disomy involving the sex chromosomes (14).

TIMING OF INTERCOURSE

The establishment of pregnancy is dependent on properly timed intercourse around the time of ovulation. Patients always ask about the optimal time and frequency of intercourse to maximize their chances. A previous study by Wilcox et al. helps to shed light on this issue (15). The investigators followed 221 women who were attempting pregnancy. All women kept track of the days they had intercourse and collected daily urine samples that were then analyzed to determine the day of ovulation. Conception occurred only when intercourse occurred in a six-day window that ended with the day of ovulation. The investigators confirmed that the greatest chance of pregnancy was when intercourse occurred beginning two days prior to ovulation (Fig. 2.3). However, some pregnancies occurred when a single act of intercourse took place five days before ovulation. No pregnancies were achieved if intercourse only took place after ovulation occurred. The investigators also looked at how the frequency of intercourse impacted on conception. The greatest chance of pregnancy was when intercourse occurred two to three times during the six-day time frame. Of interest is that lower pregnancy rates were noted when the frequency of intercourse was between four and six times during the fertile period.

DURATION OF ATTEMPTING PREGNANCY

The monthly fecundity rate in the general population has been estimated to be between 15% and 20%, which is influenced by age. A previous study by Schwartz and Mayaux reported on the cumulative pregnancy rates in 2193 women undergoing donor insemination (16). The cumulative pregnancy rates after 12 months in the <31, 31 to 35, and >35 age groups were 73%, 61%, and 54%, respectively (16). Between 78% and 85% of pregnancies that were achieved occur in the first six months of trying (17). Taking this into consideration, if a couple has failed to achieve pregnancy after six months, it seems justified to perform an infertility evaluation and even consider treatment—especially if the woman is over the age of 35. An evaluation may be indicated sooner if there is an obvious or known cause of the infertility (i.e., anovulation, previous ectopic pregnancy, etc.).

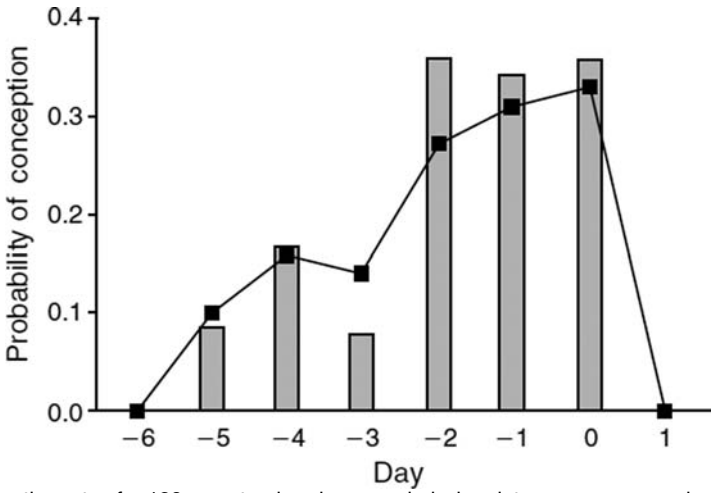

Figure 2.3 Conception rates for 129 menstrual cycles recorded when intercourse occurred on a single day. The day of ovulation is day 0. No pregnancies resulted when intercourse took place seven or more days prior to ovulation or after ovulation. The solid line is an estimate by the model for all 625 cycles. *Source*: From Ref. 15. (Reprinted from Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. N Engl J Med 1995;23:1517–21. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

OTHER FACTORS THAT IMPACT ON FERTILITY

Previous Contraception

Between 2006 and 2008, the contraceptive agents used by U.S. women (excluding sterilization) were as follows: oral contraceptives, 43%; condoms, 22%; intrauterine device (IUD), 7%; and injectables, 4% (18). The IUD was a popular method of contraception in the 1970s but one IUD in particular, the Dalkon Shield, was linked to a higher risk of pelvic inflammatory disease (PID), which increases the chance of tubal factor infertility. The design of the Dalkon Shield was the problem, and it was subsequently taken off the market and the popularity of the IUD waned but it continues to be an effective and safe method of contraception. A recent meta-analysis concluded that the risk of PID after insertion of an IUD was low but was more prevalent during the first month after insertion when there was a sixfold increase (19). The IUD is considered an option for women who have a low risk for sexually transmitted diseases. Of interest, the popularity of the IUD in the United States has increased sixfold from 1995 to 2008 (18).

The impact of the previously used contraceptive agents on future fertility has been a topic of debate. Hassan and Killick reported on the results of a survey of 2841 pregnant women who presented to antenatal clinic (20). They analyzed in the study population the time to pregnancy (TTP) for different contraceptive agents that were discontinued. They concluded that TTP was affected by the type of contraception that was previously used. The TTP for the condom, oral contraceptives, IUD, and injection was 4.6, 7.6, 7.5, and 13.6 months, respectively. The TTP results were also affected by the length of use of the oral contraceptive agents and the injectable progestational agent. For women who used oral contraceptives, the TTP was increased to 8.9 months if it was used for >4 years. For those women who used the injectable contraceptive agents, if the agent was used for <1, 1 to 2, and 2 to 4 years, the TTP was 4.5, 11.2, and 19.1 months, respectively.

Occupational Hazards

Chemical exposures can result from either an environmental exposure or more likely exposure in the workplace. The Occupational Safety and Health Administration (OSHA) regulates the workplace to insure safety for all employees. Its primary focus is on potential exposures as they relate to general health, but it has identified a number of agents that impact on reproductive health as well. Of the countless chemical exposures in the workplace, only 1000 chemicals have been evaluated for their reproductive toxicities. It is well established that exposure to nitrous oxide (N_2O) is associated with reduced fertility and spontaneous abortion (21). Since dental offices are less likely to have scavenging equipment in their offices, dental hygienists may be at particular risk (22). Exposure to other work-related chemicals (i.e., cadmium, mercury, and dry cleaning chemicals) has also been reported to decrease fertility in women.

The male is more susceptible to environmental toxins since spermatogenesis is an ongoing and dynamic process. The first report of an occupationally related spermatotoxin appeared in the mid-1970s (23). It showed that men who worked at factories that produced dibromochloropropane (DBCP; a pesticide) had an increased incidence of infertility—the severity being dependent on the dose and length of exposure. Since this report was released, other spermatotoxins that have been identified are listed in Table 2.1.

Table 2.1 Chemical Agents Shown to Alter Sperm Production

Chemical spermatotoxins	
Lead	Dibromochloropropane (DBCP)
Carbaryl	Toluenediamine
Dinitrotoluene	Ethylene dibromide
Welding	Ethylene glycol monoethyl ether
Perchloroethylene	Kepone
Bromine vapor	2,4-Dichlorophenoxy acetic acid

Diet

There is no data to suggest that any particular diet per se can impact on fertility. However, the consequences of an inadequate diet with extremes of body weight can alter ovarian function and predispose women to infertility. Women with a body mass index (BMI) <19 or body fat content <22% are at risk for hypothalamic dysfunction. At the other extreme, women with increased body weight may have associated polycystic ovarian syndrome which can cause ovulatory dysfunction. There is growing evidence that increased body weight itself may reduce fertility aside from its impact on ovulatory function. In a study published by Boston IVF, Ryley et al. performed a retrospective study of over 6000 IVF cycles (24). The conclusion was that with advanced body weight, there is a statistically significant drop in implantation and pregnancy rates. Males with an elevated BMI have been confirmed to have a greater chance of altered sperm parameters and reduced fertility.

Lifestyle Habits

There are many lifestyle habits can impact our general health, and there is reason to believe that they may also impact on fertility.

Smoking

Of all the lifestyle issues, smoking is the most significant. Smoking is a confirmed reproductive toxin. The deleterious effects of smoking during pregnancy are well established. Several published studies have demonstrated that smoking in women is associated with decreased fertility (25,26). Smoking reduces a woman's chances of conceiving by almost half. Smoking can alter ovarian function in a number of ways (27). The chemicals in smoke stimulate the hepatic metabolism of steroid hormones, thereby reducing their levels in the blood stream. In vitro studies have demonstrated that the chemicals in smoke alter the enzymes that are necessary for ovarian hormone production. Finally, women who smoke generally go through an earlier menopause by one to two years, suggesting that the chemicals in smoke may be directly toxic to the ovaries. It is not known whether this is due to a direct action on the ovaries or indirectly through an alteration of the blood flow to the ovary. The published data is compelling enough to advise all women to stop smoking to improve their fertility.

Caffeine

Caffeine use has been associated with an increased risk of pregnancy loss (28). There have been several reports linking a woman's caffeine intake to decreased fertility when controlling for other factors (29,30). A dose-dependent relationship has been confirmed, which suggests that any amount of caffeine consumption could be detrimental to fertility.

Alcohol

The ill effects of alcohol on pregnancy are well established. However, the influence of alcohol on fertility has not been well studied. In 1998, two separate studies were published that examined the impact of alcohol on the establishment of pregnancy (31,32). Both studies arrived at the same conclusion that alcohol, in a dose-dependent fashion, reduced the chance of a conception in the study populations. There are no published data that suggest that moderate alcohol use affects male reproduction.

A previous study by Hassan and Killick lends further support that a healthy lifestyle improves fertility (33). The investigators looked at the combined effects of lifestyle issues on the establishment of a pregnancy. Over 2000 women who presented for prenatal care were asked about lifestyle issues, and then the investigators determined the TTP. The investigators confirmed that the TTP was delayed if the woman or her partner smoked, the partner consumed >20 units of alcohol per week, caffeine intake was >6 per day, and the woman's BMI was >25 kg/m^2. Since many couples had multiple factors, the authors calculated the cumulative pregnancy rate when more than one factor was present (Fig. 2.4).

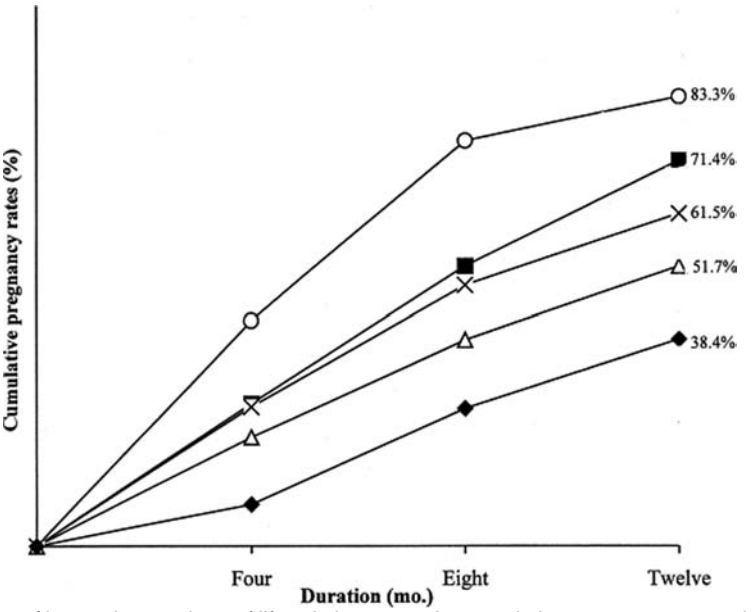

Figure 2.4 Effect of increasing numbers of lifestyle issues on the cumulative pregnancy rates within one year for a pregnant population. The lifestyle variables are presented in the box adjacent to the graph. Each line is the cumulative pregnancy rate for subgroups with different numbers of negative lifestyle variables: ○, No negative variables; ■, one negative variable; X, two negative variables; △, three negative variables; ◆, four or more negative variables. *Source*: From Ref. 33. (Reprinted from Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004;81:384–92 with permission from the American Society for Reproductive Medicine.)

Stress and Anxiety

There continues to be an ongoing debate about the role of stress in infertility. Lingering questions continue: Is stress a cause of infertility? Can stress decrease a woman's chance of pregnancy while undergoing treatment? For those patients who are stressed, what interventions are effective? There is no doubt that most patients that are seen at fertility clinics are stressed. For some patients, the stress and/or anxiety preceded their desire for pregnancy, whereas for others it worsened or developed newly as a reaction to the disappointment of their situation. The stress associated with infertility is intense and is similar to the stress associated with a serious medical condition such as cancer or HIV. In a previous study, it was reported that up to 40% of infertile women had anxiety and/or depression (34). This is significant when one considers the incidence of anxiety/depression in the general population which is 3%. Does the stress prevent a patient from achieving pregnancy? Many of us have firsthand stories about patients who conceive after a relaxing vacation or women who have battled years of infertility and then proceed with a successful adoption and then are surprised to learn that they have achieved pregnancy on their own. These situations no doubt raise suspicion. While it may be difficult to prove that stress is a cause of infertility, there is data to suggest that it may reduce the chance of success with treatment. In a previous review, most of the published studies examining this issue concluded that anxiety and stress reduced a patient's chance of success with treatment (35). Another publication, the largest investigation to date, reported on a prospective study that involved 818 couples who were screened with a stress inventory at the start of treatment and then 12 months later treatment outcomes were determined. After controlling for female age and years of infertility, the authors concluded that female and male stress affected the outcome of the treatment. There are different interventions we can offer our patients to counter the stress. Those that offer cognitive-behavioral intervention seem to be the most effective in decreasing anxiety and improving success rates (36,37). While significant progress has been made, further research is needed to provide a better understanding of the role of stress.

CONCLUSIONS

There are many factors that ultimately impact on a couple's chances of conceiving naturally or with a reproductive technology. While some factors can be altered thereby increasing the chances of pregnancy, others cannot. The single most important factor that impacts on a couple's chances of conceiving is the woman's age. A major challenge we face in reproductive medicine is to educate the populace about the impact of age, thereby preventing some women from delaying childbearing for too long.

REFERENCES

1. Mathews TJ, Hamilton BE. Delayed Childbearing: More Women Are Having Their First Child Later in Life. Hyattsville, MD: National Center for Health Statistics; 2009. NCHS Data Brief; No. 21.
2. Coale AJ, Trussell TJ. Model fertility schedules: variations in the age structure of childbearing in human populations. Popul Index 1974; 40:185–256.
3. Faddy MJ, Gosden RG, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992; 7:1342–1346.
4. Johnson J, Canning J, Kaneko T, et al. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 2004; 428:145–150.
5. Munne S, Alikani M, Tomkin G, et al. Embryo morphology, developmental rates and maternal age are correlated with chromosome abnormalities. Fertil Steril 1995; 64:382–391.
6. Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249:2034–2038.
7. Kidd SA, Eskenzazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. Fertil Steril 2001; 75:237–248.
8. Kühnert B, Nieschlag E. Reproductive functions of the ageing male. Hum Reprod Update 2004; 10(4):327–339.
9. Vermeulen A. Androgens in the aging male. J Clin Endocrinol Metab 1991; 73:221–224.
10. Goemaere S, Van Pottelbergh I, Zmierczak H, et al. Inverse association between bone turnover rate and bone mineral density in community-dwelling men >70 years of age: no major role of sex steroid status. Bone 2001; 29:286–291.
11. Seymour FI, Duffy C, Koerner A. A case of authenticated fertility in a man, aged 94. J Am Med Assoc 1935; 105:1423–1424.
12. Dain L, Auslander R, Dirnfeld M. The effect of paternal age on assisted reproduction outcome. Fertil Steril 2011; 95:1–8.
13. Luetjens CM, Rolf C, Gassner P, et al. Sperm aneuploidy rates in younger and older men. Hum Reprod 2002; 17:1826–1832.
14. Lowe X, Eskenazi B, Nelson DO, et al. Frequency of XY sperm increase with age in fathers of boys with Klinefelters syndrome. Am J Hum Genet 2001; 69:1046–1054.
15. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. N Engl J Med 1995; 23:1517–1521.
16. Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination of 2193 nulliparous women with azoospermic husbands. Federation CECOS. N Engl J Med 1982; 306(7):404–406.
17. Ford WCL, North K, Taylor H, et al. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. Hum Reprod 2000; 15:1703–1708.
18. Use of Contraception in the United States: 1982–2008. Hyattsville, MD: Center for Disease Control (CDC); 2010. Vital & Health Statistics; Series 23; No. 29.
19. Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion (Cochrane Review). In: The Cochrane Library, Issue 3. Chichester, UK: John Wiley & Sons, Ltd, 2004.
20. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? Hum Reprod 2004; 19:344–351.
21. Cohen EN, Gift HC, Brown BW, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980; 101:21–31.
22. Rowland AS, Baird DD, Weinber CR, et al. Reduced fertility among women employed as dental assistants exposed to high level so nitrous oxide. N Engl J Med 1992; 327(14):993–997.
23. Cohen EN, Bellville JW, Brown BW Jr. Anesthesia, pregnancy and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology 1971; 35:343–347.
24. Ryley DA, Bayer SR, Eaton A, et al. Influence of body mass index (BMI) on the outcome of 6,827 IVF cycles. Fertil Steril 2004; 82:S38–S39.

25. De Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. Int J Epidemiol 1988; 17:378–384.
26. Bolumar F, Olsen J, Boldsen J. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. Am J Epidemiol 1996; 143:578–587.
27. Smoking and Women's Health. Washington, DC: American College of Obstetricians & Gynecologists; 1997. Education Bulletin; No. 240.
28. Tolstrup JS, Kjaer SK, Munk C, et al. Does caffeine and alcohol intake before pregnancy predict the occurrence of spontaneous abortion? Hum Reprod 2003; 18:2704–2710.
29. Hatch EE, Bracken MB. Association of delayed conceptions with caffeine consumption. Am J Epidemiol 1993; 38:1082–1092.
30. Bolumar F, Olsen J, Rebagliato M, et al. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. Am J Epidemiol 1997; 145:324–334.
31. Jensen TK, Hjollund NHI, Henriksen TB, et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. Br Med J 1998; 317:505–510.
32. Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. Fertil Steril 1998; 70:632–637.
33. Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004; 81:384–392.
34. Chen TH, Chang SP, Tsai CF, et al. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004; 19:2313–2318.
35. Domar AD. Infertility and the mind/body connection. Female Patient 2005; 30:24–28.
36. Tuschen-Caffier B, Florin I, Karuse W, et al. Cognitive-behavioral therapy for idiopathic infertile couples. Psychother Psychosom 1999; 68:15–21.
37. Domar AD, Clapp D, Slawsby EA, et al. Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 2000; 73:805–811.

3 The infertility workup

Steven R Bayer and Michael M Alper

INTRODUCTION

A complete infertility workup is a prerequisite before a treatment plan can be developed. The workup has changed dramatically over the years. In the past, the testing could span several months and entailed numerous tests that in retrospect were unreliable and are now considered unnecessary. Presently, the workup is streamlined, focused, and can be completed within a month so that treatment can be started expeditiously. This chapter reviews the approach to the workup of the infertile couple.

OBJECTIVES OF THE INITIAL INTERVIEW

Since infertility is a problem that affects the couple, it is important that both partners are present for the initial interview and when decisions are made regarding treatment. Like any doctor-patient relationship, it is important to establish good rapport, but this is even more critical when one is caring for the infertile couple. As a result of the psychological component that accompanies this diagnosis, patients with infertility require a much more demanding relationship than is typically required with other gynecological patients. The initial consultation is an extremely important encounter, and an adequate amount of time (30–60 minutes) should be spent with the couple. There are several objectives of the initial interview, which are described below.

Determine the Necessity of an Evaluation

The first step is to make sure that an evaluation is indicated. The physician must determine whether the couple has had well-timed intercourse and they have been trying for a sufficient duration of time. Although the classic definition of infertility is the lack of pregnancy after one year of unprotected intercourse, it is appropriate to initiate an evaluation after six months of infertility, or sooner if the woman is older (>35 years of age) or when there is an obvious cause of the infertility (ovulatory dysfunction, known tubal disease, endometriosis, etc.). In fact, about 80% of pregnancies are achieved within six months of unprotected intercourse. So, inability to conceive by six months is a reason to initiate an evaluation.

Educate the Couple

It is important to educate the couple on normal reproductive function. For many couples, the last time they had formal instruction on reproduction was in high school during sex education classes and much of their knowledge may not be factual. Diagrams may be helpful in achieving the education process. A basic knowledge of the normal reproductive process helps the couple better understand the various causes of infertility, the rationale of the evaluation, and the treatment that may be recommended. It is also important to emphasize to the couple that our reproductive systems are inefficient, and even in optimal situations, a normal fertile couple can only expect a 15% to 20% chance of pregnancy per month. This will help them put treatment success rates in the right perspective.

Identify Risk Factors

Another objective of the initial interview is to identify risk factors that may explain the infertility and provide focus to the workup. A history of irregular menstrual cycles is suggestive of an ovulatory problem. Previous use of an intrauterine device (IUD), a history of a tubal pregnancy, or a pelvic infection can raise suspicion of a tubal factor. Complaints of worsening dysmenorrhea or dyspareunia may suggest the presence of endometriosis. Previous cryosurgery, conization, or the loop electrosurgical excision procedure (LEEP) of the cervix increases the chance of a cervical factor.

Preconceptional Care

An important part of the initial consultation is a discussion on preconceptional care. This involves a review of medical, environmental, nutritional, social, and genetic issues that may impact on fertility and complicate the outcome of a pregnancy. In some cases, the particular issue of concern must be investigated before proceeding with any treatment. An in-depth discussion of preconceptional care appears in chapter 4 of this book.

Psychological Assessment

At some point during the initial interview, the couple should be asked about how they are dealing with the stress of their plight. Patients always put on their best faces when in front of the physician, but when they are asked about the stress, many times it becomes quite apparent that the stress is often significant. It should be emphasized to the couple that all couples experience stress to some degree. For many couples, infertility may be the most stressful situation that they have had to deal with in their lives. The clinician should have mental health professionals that the couple can be referred to. In some cases, a referral may be indicated early in the process even during the initial evaluation.

Treatment Plan

At the end of the consultation, a plan for evaluation should be discussed with the couple. The couple should have a good understanding about the scope of the evaluation and the rationale for the tests that have been selected. Since most patients will be unable to absorb and remember all what was discussed, written material should be given to the couple describing the tests that will be performed. Finally, the couple should be given an estimate of the length of time to complete the evaluation and when to schedule a follow-up appointment to discuss the results and begin discussions about treatment.

CAUSES OF INFERTILITY

The objective of the infertility evaluation is to identify specific cause(s) of the infertility, which will allow the clinician to administer the appropriate treatment (Fig. 3.1). In the past, the infertility evaluation involved performing several tests including the semen analysis, hysterosalpingogram (HSG), postcoital test, endometrial biopsy, and a laparoscopy. During the course of the evaluation, it was not uncommon that the postcoital test and endometrial biopsy were repeated multiple times; however, published studies have confirmed that the postcoital and endometrial biopsy tests are unreliable and do not differentiate between fertile and infertile populations. Similarly, it was also common practice to perform a laparoscopy routinely before any therapy was started. However, we now realize that, in most cases, the findings at the time of the laparoscopy do not change the course of recommended treatment. To this end, the infertility evaluation has been simplified and includes a cycle day 3 follicle-stimulating hormone (FSH)/estradiol, HSG, and a semen analysis. A discussion of the various causes of infertility and the current infertility evaluation is presented. The reader is also referred to chapter 5 where clinical algorithms are presented.

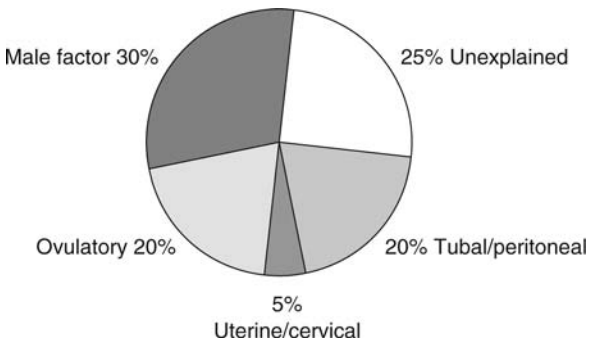

Figure 3.1 Causes of infertility.

Ovarian Function

One of the first steps in the infertility evaluation is to assess ovarian function. Significant information can be obtained from the menstrual history including the age at menarche, frequency of menstrual cycles in the present and past, and the duration of menstrual flow. Important aspects of ovarian function related to fertility are discussed below.

Determination of Whether Ovulation Is Occurring

If a woman is having regular menstrual cycles that are 23 to 39 days in length, then she is most likely ovulating. This is further supported if the bleeding is preceded by premenstrual symptoms (i.e., water weight gain, breast tenderness, and mood changes). If there is any doubt about a woman's ovulatory status, then a simple inexpensive test is to have her keep a daily record of her temperature [basal body temperature (BBT) record]. The progesterone that is secreted by the corpus luteum during the luteal phase acts on the temperature-regulating center in the hypothalamus causing an increase in the basal temperature from 0.5°F to 1.0°F. Previously, women were instructed to take temperature readings upon wakening; however, the temperature can also be taken at other times of the day as long as it is done on a consistent basis. Another way to confirm ovulation is with the ovulation predictor kits that are widely available. Finally, a serum progesterone level >3 ng/mL is yet another confirmatory test that ovulation has taken place.

Assessment of Ovarian Reserve

During a woman's lifetime, the maximum number of oocytes (approximately 6–7 million) residing in the follicles is present in utero at 20 weeks of gestation. From that time forward and throughout a woman's lifetime, there is a continuum of ovarian follicular development that occurs, and if the follicle at its critical stage of development is not rescued by a threshold level of FSH, it undergoes atresia. The decrease in the number of oocytes is significant—at birth the number is decreased to 1 to 2 million and at puberty to 600,000, to 700,000. Less than 0.01% of eggs a woman is endowed with ever have a chance of ovulating. Ultimately, there is total depletion of the oocytes and menopause results. It must be realized that menopause is not an abrupt process but represents an end point of a transitional process that spans several years. One of the first changes that a woman can notice as she approaches menopause is a gradual shortening of the menstrual cycle, which is the result of a shorter follicular phase. In addition, early follicular phase FSH and estradiol levels also can identify women who are starting to approach the menopausal transition. Assessment of ovarian reserve is an important part of the infertility workup, and there are several ways to accomplish it as described below.

1. ***Basal FSH and estradiol*:** The most common and easiest means of testing ovarian reserve is measuring an FSH and estradiol level between cycle days 2 and 4. To interpret the FSH level, an estradiol level must also be checked, since an elevated estradiol through negative feedback can suppress the FSH level to the normal range. If the FSH level is >10 mIU/mL or the estradiol is >70 pg/mL, then it can be concluded that the woman has reduced ovarian reserve (Table 3.1). There can be cycle to cycle variation in the FSH and estradiol levels, but a single elevation is predictive of reduced ovarian reserve.
2. ***Clomiphene citrate challenge test (CCCT)*:** CCCT is a dynamic test used to examine ovarian reserve. Clomiphene citrate is a weak estrogen agonist/antagonist that binds to

Table 3.1 Interpretation of Cycle Day 3 Hormone Levels

FSH level (mIU/mL)	Estradiol level (pg/mL)	Ovarian reserve
>10	<70	Reduced
>10	>70	Reduced
2–10	>70	Reduced
2–10	<70	Normal

estrogen receptors in the hypothalamus, which results in the release of FSH and luteinizing hormone (LH) from pituitary gonadotrophs. The test is performed as follows:

- Cycle day 3: FSH and estradiol levels
- Clomiphene citrate 100 mg daily between cycle days 5 and 9
- Cycle day 10: FSH level

If either of the FSH levels is >10 mIU/mL or the day 3 estradiol is >70 pg/mL, reduced ovarian reserve may be present. CCCT can be more informative since 75% of women with reduced ovarian reserve have a normal cycle day 3 hormone assessment. We generally use this test in all women over the age of 40 and younger women when indicated (family history of premature ovarian failure, previous ovarian surgeries, and short menstrual cycles).

3. ***Antral follicle count (AFC)*:** Assessment of the AFC by vaginal ultrasound has evolved into another test to evaluate ovarian reserve and was reviewed in a recent publication (1). A vaginal ultrasound is performed on cycle day 3 and the number of antral follicles is determined. The definition of an antral follicle has not been standardized. Some investigators have considered an antral follicle to be between 2 and 5 mm, while others have used the maximum diameter up to 10 mm. If a center uses this method, then it must be standardized and correlated with their outcome. Hendriks et al. (1) published a meta-analysis on the AFC and confirmed that AFC is superior to the cycle day 3 FSH level in predicting ovarian response. However, neither test was good at predicting the absence of the establishment of a pregnancy.
4. ***Anti-Müllerian hormone (AMH) level*:** AMH is another test that is available to access ovarian reserve. During embryogenesis, AMH plays an important role in guiding male sexual differentiation and also plays a role in female reproduction. It is produced by the granulosa cells of preantral follicles, and it inhibits early stages of follicular development. The level of the AMH is directly indicative of the remaining follicular pool. AMH levels begin decreasing around age 30. Normal levels of AMH are from 1 to 3 ng/mL, and levels <1 ng/mL suggest reduced ovarian reserve but one must take into account the patient's age (Fig. 3.2). Higher AMH levels >3 ng/mL have been noted in patients with polycystic ovarian syndrome (PCOS). The AMH level does not vary during the menstrual cycle, so it can be measured at any time.

   In a previous study, AMH, FSH, and inhibin levels were measured retrospectively in a group of 93 patients who underwent 123 cycles of in vitro fertilization (IVF) (3). The IVF cycles were separated into those with ≤4 eggs and those with >4 eggs. AMH was superior in predicting outcome compared to FSH and inhibin levels. When the AMH level was <0.83 ng/mL, the sensitivity and specificity for predicting a reduced number of eggs (≤4 eggs) was 83% and 79%, respectively. However, the predictive value of a positive test (AMH < 0.83) in predicting <4 eggs was only 30%.
5. ***Exogenous FSH ovarian reserve test (EFORT)*:** This test was described by Fanchin et al. (4). The test is performed as follows: on cycle day 3, FSH and estradiol levels are checked and the patient is given a single injection of FSH 300 IU. On cycle day 4, an estradiol level is checked. They defined normal ovarian reserve when the FSH was <11 mIU/mL and the estradiol was >30 pg/mL. This testing has not been investigated extensively and is not widely used in the clinical setting.

How do we counsel the woman who has reduced ovarian reserve? In the past as we were getting a handle on the concept of ovarian reserve, it was not uncommon that a patient with an FSH level over a certain threshold was not allowed to undergo treatment with IVF. However, an elevated FSH level in a 42-year-old woman with unexplained infertility means something different than an elevated FSH level in a 25-year-old woman. A previous publication by Abdalla and Thum helps to put this into better perspective (5). The investigators reported on 2057 patients who underwent their first IVF cycle. The policy in their clinic was that all women with regular menstrual cycles were considered candidates for IVF treatment. There were several conclusions of their study.

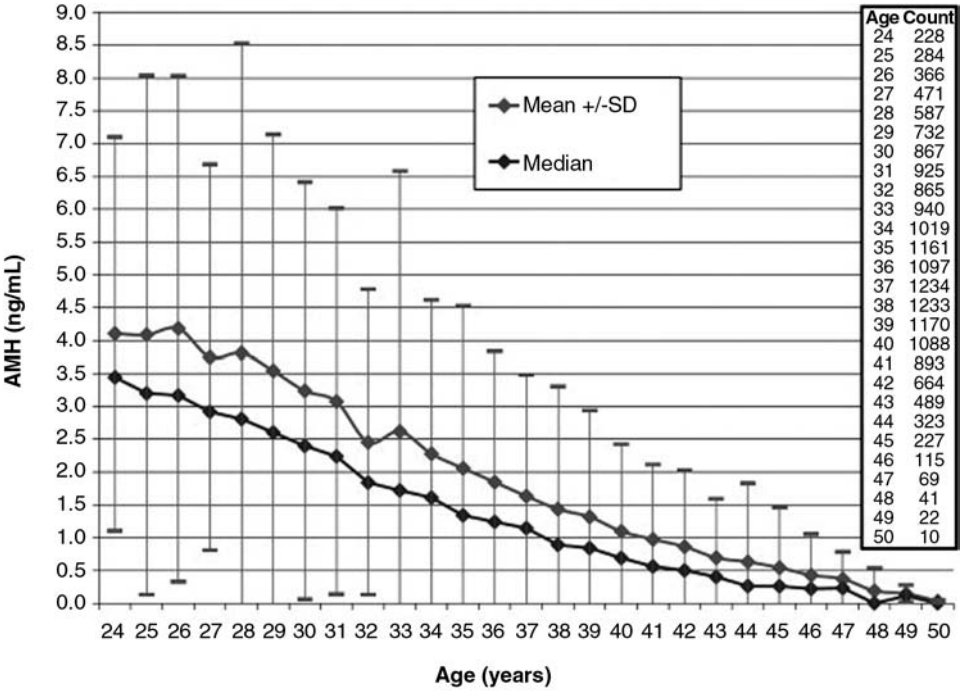

Figure 3.2 Age versus AMH levels. *Abbreviation*: AMH, Anti-Müllerian hormone. *Source*: From Ref. 2. (Reprinted from Seifer DB, Baker VL, Leader B. Age-Specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril 2011;95:747–50 with permission from the American Society for Reproductive Medicine).

1. An elevated FSH level (irrespective of age) was associated with a reduced pregnancy rate.
2. The fertilization rate was not affected by the FSH level.
3. The chance of a pregnancy loss was impacted on by age and not the FSH level.
4. An elevated FSH level is indicative of oocyte number not quality.
5. A younger woman with an elevated FSH had a significantly higher chance of a successful pregnancy as compared to an older woman with a normal FSH level (21.2% vs. 12.1%).

Ovarian reserve testing is an important part of the infertility evaluation but it must be realized that the testing is not definitive but should be viewed as a ***screening test*** *of ovarian reserve. Therefore, the results of the testing should not be used solely in the determination of whether to allow a patient to undergo treatment. The true test of ovarian reserve is a stimulated cycle. While this information is helpful in the counseling of patients, there are other factors including age, previous response to ovarian stimulation, and prior outcome of treatment that must be taken into consideration.*

Evaluation of the Woman with Ovulatory Dysfunction

Ovulatory dysfunction is present in a woman who has menstrual cycles that are out of the normal range (25–35 days). The initial workup should include measurement of thyroid-stimulating hormone (TSH), prolactin, and cycle day 3 FSH and estradiol levels. Prolactin levels fluctuate throughout the day reaching a nadir in the morning and tend to be higher in the luteal phase. Therefore, it is important that the prolactin determination be performed on a morning follicular phase blood sample. If the woman has symptoms of hyperandrogenism, then additional testing is indicated. This should include a determination of testosterone, dehydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone (17-OHP) levels. The 17-OHP determination should also be performed on a morning follicular phase blood sample because the corpus luteum produces

17-OHP. There is substantial evidence that insulin resistance is a cause of PCOS. There is no reliable practical test to confirm insulin resistance. Some have used the glucose-to-insulin ratio or simply the insulin level to gauge the degree of insulin resistance. Insulin resistance can lead to glucose intolerance. Therefore, in patients with PCOS, in addition to the androgen studies, a fasting glucose or hemoglobin A1C should be measured to rule out glucose intolerance. The clinical presentation and the laboratory studies will help to determine the cause of the ovulatory dysfunction, which can be varied and secondary to hypothalamic dysfunction (reduced weight), chronic anovulation (polycystic ovarian disease), and impending ovarian failure.

Luteal Phase Deficiency

In the past, there was a belief that luteal phase deficiency was a cause of infertility and recurrent miscarriages. It was theorized that some women may be ovulating and having regular menstrual cycles but the progesterone secreted during the luteal phase is insufficient to mature the endometrium for implantation or unable to support a pregnancy. There were two approaches to evaluate the adequacy of the luteal phase. The first was measuring a mid-luteal phase progesterone level. A progesterone level below 10 ng/mL was suggestive of a progesterone deficiency. The major difficulty with using progesterone levels in this fashion is that progesterone is secreted in pulses every two to three hours, which will interfere with the interpretation of a single level (6). The more popular technique to assess the adequacy of the luteal phase was an endometrial biopsy performed late in the luteal phase. It was thought that the endometrial biopsy represented a bioassay of all of the progesterone that was secreted during the luteal phase. Progesterone secreted in the luteal phase causes day-by-day changes in the endometrium that can be appreciated histologically. A luteal phase deficiency was established if there was at least a three-day lag between the histological date of the endometrial biopsy and the chronological date of the menstrual cycle (established retrospectively with the knowledge of the onset of the next menses and assuming a 14-day luteal phase). From a theoretical standpoint, this makes good sense, but there are problems with the endometrial biopsy for assessment of the luteal phase, including the following:

1. Uncertainty when the menstrual period begins, which would interfere with the establishment of the chronological day.
2. Interobserver variation in the pathological interpretation of the biopsy.
3. The false premise that the luteal phase is 14 days in length, which can actually range between 13 and 16 days.

In a previously published study, Coutifaris and coworkers shed more light on the use of the endometrial biopsy for infertility testing (7). The study was a prospective multicenter study that involved 847 subjects, both fertile and infertile. A total of 42.2% of the fertile women and 32.7% of the infertile women tested had an out-of-phase biopsy (>2 days out of phase). Paradoxically, the fertile group had a greater chance of having an abnormal test result. Other studies have also supported that the endometrial biopsy is an invalid test (8–10). After reviewing the published studies, the assessment of the luteal phase should not be a part of the infertility evaluation.

Cervical Factor Infertility

The cervix plays an important role in reproductive physiology. It provides the passageway for sperm, allowing them access into the uterine cavity and ultimately the fallopian tubes. The ability of the sperm to gain access to the upper tract is influenced by the cervical mucus that is present in the cervical canal. The estradiol that is produced by the preovulatory follicle increases the quantity and consistency of the mucus produced by the endocervical glands. Estradiol increases the water content of the mucus that reaches a peak of 95% to 98% at mid-cycle. In the days that precede ovulation, a thin, watery mucus spills out of the cervical canal and covers the portio of the cervix and upper vagina. Some women notice this change in the cervical mucus, whereas others do not. If intercourse occurs during this time period, the sperm are able to penetrate the mucus and survive for up to three days or more. In contrast, during the early follicular phase when the estradiol levels are low or in the luteal phase when any

estrogenic affect is counteracted by progesterone, the cervical mucus is thick and tenacious. If intercourse occurs at these times, the sperm are unable to penetrate this poor-quality mucus and the sperm die in the vagina within a few hours because of its acidic environment.

Impaired sperm penetration of the cervical mucus following intercourse can prevent the establishment of pregnancy. The etiology of this condition is varied and can be secondary to faulty coital technique, inadequate cervical mucus production, or poor-quality sperm. Less than 5% of infertile couples will have a cervical factor as the cause of their infertility (excluding couples with a contributory male factor). A history of LEEP or ablative surgery to the cervix can put the woman at risk for a cervical factor. It is also important to ask couples about the use of lubricants during intercourse. Some over-the-counter lubricants can impair sperm motility but other safer lubricants are available.

The Postcoital Test

The postcoital test is the diagnostic test that has been used to assess the functional capacity of the cervix as it relates to fertility. This test is an evaluation of the quality of the cervical mucus and a determination of the number of sperm that have penetrated the mucus. There has been controversy about the test in part because it has never been standardized. Further, published data have confirmed that the postcoital test is unreliable and does not differentiate between fertile and infertile couples (11).

It is our opinion that the postcoital test should not be part of the routine evaluation. However, an examination of the cervical mucus during the preovulatory period may be indicated in the woman who has had a destructive procedure performed on the cervix, which may compromise cervical mucus production.

Male Factor Infertility

Male factor infertility is identified in approximately 30% of infertile couples. At the initial consultation, it is important that an in-depth medical history is obtained from the male partner. Previous surgery for repair of an inguinal hernia could have resulted in inadvertent injury to the vas deferens, which courses through the inguinal canal. A history of cryptorchidism can be associated with altered testicular function. Chronic illnesses (i.e., chronic renal disease, thyroid dysfunction, diabetes mellitus, and malnourished states) can also impair normal spermatogenesis. A neuropathy can complicate diabetes and can result in the development of impotence or retrograde ejaculation. A medication history is also important. Sulfasalizine can be prescribed for ulcerative colitis and can cause a decrease in sperm concentration and motility, which will resolve after the medication is discontinued. The antimitotic activity of colchicine, a medication prescribed for gout, can also decrease sperm production. Some medications that are used to treat hypertension and mood disorders have sympathetic or parasympathetic actions that can interfere with erectile function and/or ejaculation. Male bodybuilders should be questioned about the use of anabolic steroids and other oral hormonal agents that can result in significant oligospermia and in some cases azoospermia, which are reversible. Other medications that can impact on male reproduction include the following: cimetidine, spironolactone, isoniazid, calcium channel blockers, and chemotherapeutic drugs. Recreational drugs such as alcohol, tobacco, and marijuana if taken in excess can also be detrimental. Spermatogenesis is a temperature-sensitive process and the scrotal temperature is generally 2°F to 3°F lower than core body temperature. Hot tubs, saunas, or a febrile illness can increase the temperature of the testes and can impair sperm production. Finally, the male should be questioned regarding chemical exposures at the workplace. Exposure to insecticides, pesticides, lead, and organic solvents, among others, have been shown to impact on male fertility.

The semen analysis has been the standard test for the evaluation of the male partner. The male partner is instructed to abstain from ejaculation for two days prior to performance of the test. The specimen is produced by masturbation. Depending on the laboratory facility, the specimen can be produced on site. If the couple lives within 45 minutes of the laboratory, then the sample can be produced at home and then transported to the laboratory for the analysis. During transport, it is important that the sample is kept at body temperature. The normal parameters of the semen analysis are given in Table 3.2.

Table 3.2 Normal Parameters of Semen Analysis

Volume	2–5 cc
Sperm count	>20 million sperm/cc
Motility	>50%
Morphology	>4% normal forms (by Krüger classification) >40% normal forms (by World Health Organization criteria)
Liquefaction time	15–30 min

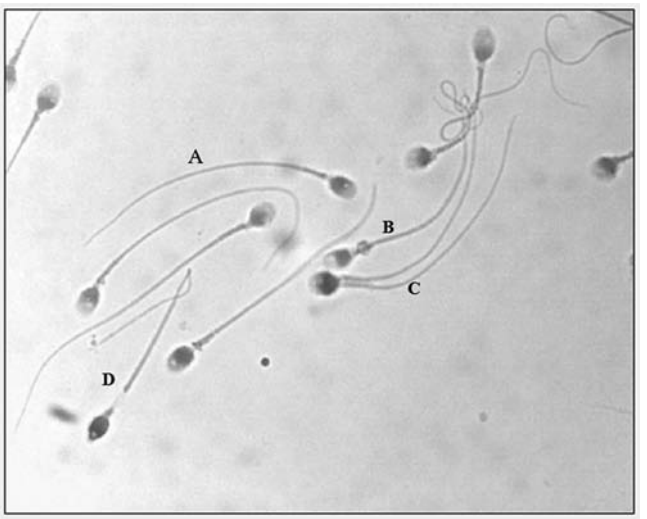

Figure 3.3 Examples of varied sperm morphology: A, normal; B, midpiece defect; C, tail defect; D, tapered head.

An important assessment of the semen analysis is a determination of the percentage of sperm with normal morphology (Fig. 3.3). The World Health Organization (WHO) classification system has been used to evaluate sperm morphology and a sample is considered normal if >40% of the sperm have normal morphology. Presently, the Tygerberg classification (also called the Krüger classification) is widely used and is a more critical assessment of sperm morphology. By this classification, a sample is considered normal if >4% of the sperm have normal morphology. It must be realized that the assessment of the morphology is subjective on the part of the laboratory technician and variations in interpretation may occur from laboratory to laboratory. Since a semen analysis is a specialized test, it is important to select an experienced laboratory to perform the test. The reliability of the interpretation of a semen sample will be proportional to the number of specimens that are handled by any particular laboratory.

It is important to realize that the semen analysis is a quantitative assessment of the semen sample. Further, the normal ranges established for the various parameters are somewhat arbitrary, and a previous study confirmed overlap between the semen parameters in a fertile and infertile population (12) (Fig. 3.4). Unfortunately, we do not have a test that provides a qualitative assessment of sperm function short of in vitro fertilization or pregnancy itself. Several years ago, the hamster penetration assay was touted as a qualitative test of sperm function, but numerous studies have disproved its reliability and we do not feel that it has any use in the evaluation of the male infertility.

If the semen analysis is normal, then no further workup of the male partner is indicated. If the semen analysis is abnormal, then a repeat sample should be obtained two to four weeks later. There is day-to-day variability of the semen parameters. Further, an abnormal semen analysis might be explained by a stressful event (i.e., febrile illness) that occurred two to three months prior to the time of the initial semen analysis. This is the amount of time it takes for mature sperm to develop. If the repeat semen analysis is abnormal, then a referral to a urologist

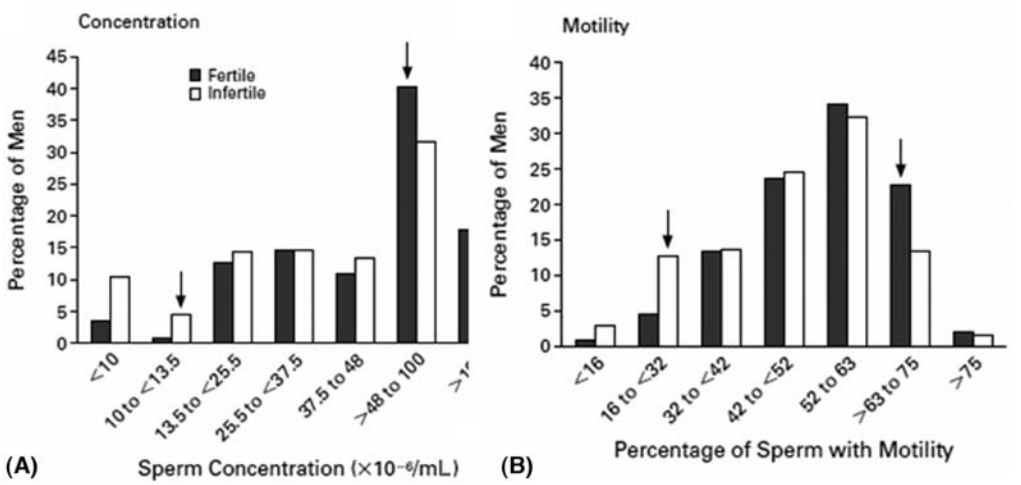

Figure 3.4 Comparison of semen parameters (concentration and motility) between men of fertile and infertile couples. In each panel, the left arrow separates infertile and indeterminate groups and the right arrow separates indeterminate from fertile groups. (Reprinted from Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388-93. Copyright © 2001 Massachusetts Medical Society. All rights reserved.)

is indicated for further evaluation. One important reason a referral is that a presenting sign of testicular cancer may be an abnormal semen analysis (13,14). On examination by the urologist, a varicocele may be identified. A varicocele is a dilated scrotal vein, which can be identified in up to 40% of infertile males but can also be present in 15% of normal fertile males (15). There are several theories that have been proposed to explain the association between a varicocele and male infertility. The most accepted theory is that the dilated testicular vein raises the temperature of the testes, which alters sperm production. However, there continues to be controversy about the association of a varicocele and infertility, and the benefits of surgical correction. The reported pregnancy rates following surgical ligation of a varicocele are between 30% and 50%. However, a meta-analysis of pertinent studies failed to demonstrate any improvement in male fertility following a varicocele ligation (16).

Laboratory studies (FSH, LH, testosterone, and prolactin) may help to rule out an endocrinopathy, which could explain significantly impaired spermatogenesis. If the gonadotropins (FSH, LH) are depressed or undetectable, this may suggest the presence of either Kallman's syndrome or hypothalamic dysfunction, which can be corrected with FSH and human chorionic gonadotropin (hCG) injections. An elevated FSH level suggests the presence of testicular failure that is usually unexplained but may be secondary to Klinefelter's syndrome (47, XXY), Sertoli-cell-only syndrome, previous mumps orchitis, or prior cancer treatment. A karyotype is indicated in cases of azoospermia (associated with an elevated FSH) and severe oligospermia when the sperm concentration is <5,000,000 sperm/cc. The incidence of an abnormal karyotype is 10% to 15% of men with nonobstructive azoospermia and 5% of men with severe oligospermia (17). Microdeletion studies of the Y chromosome should be performed on males with severe oligospermia. The Y chromosome microdeletions are present in 10% to 15% of men with severe oligospermia (18). Understanding the underlying genetic basis for oligospermia is important for genetic counseling purposes. Genetic testing in men with severe oligospermia is indicated and should be a prerequisite prior to proceeding with IVF and intracytoplasmic sperm injection (ICSI). An abnormal genetic test should trigger a referral to a genetic counselor. Hyperprolactinemia is uncommon in the male but can be associated with impotence. In the male with azoospermia and normal gonadotropins, one must consider either the presence of an obstructed outflow tract or congenital absence of the vas deferens as the cause. Often the diagnosis can be made on physical examination, but a testicular biopsy with a vasogram may be helpful. While a physical examination and laboratory evaluation are helpful to evaluate the male with abnormal semen parameters, the majority of cases remain unexplained.

Tubal Factor Infertility

Tubal factor infertility is present in approximately 20% of infertile women. Risk factors include a previous ectopic pregnancy, ruptured appendix, previous use of an IUD, or a history of pelvic inflammatory disease. Even so, the majority of women who are found to have a tubal factor do not have any risk factor. These cases are most likely the result of an asymptomatic pelvic infection.

The HSG is the standard test to assess tubal patency (Figs. 3.5 and 3.6). This test is performed early in the follicular phase after the cessation of menstrual flow. It is safer to use a water-based medium for the examination. Absolute contraindications for performing the test are suspicion of pregnancy and active pelvic infection. If a patient states that her previous menses was lighter or delayed, then a pregnancy test should be done prior to the X ray. A complication following an HSG is an infection, which has an incidence of 1% to 3% (19). The rate of infection is 11% following an HSG in those patients with confirmed distally blocked tubes. For this reason, antibiotics (doxycycline 100 mg po bid x 5 days) should be given prophylactically to women with known tubal disease prior to an HSG or following an HSG when tubal pathology has been confirmed. Routine antibiotic administration prior to an HSG is not recommended (20). An allergic reaction following an HSG is rare, since the iodine dye does

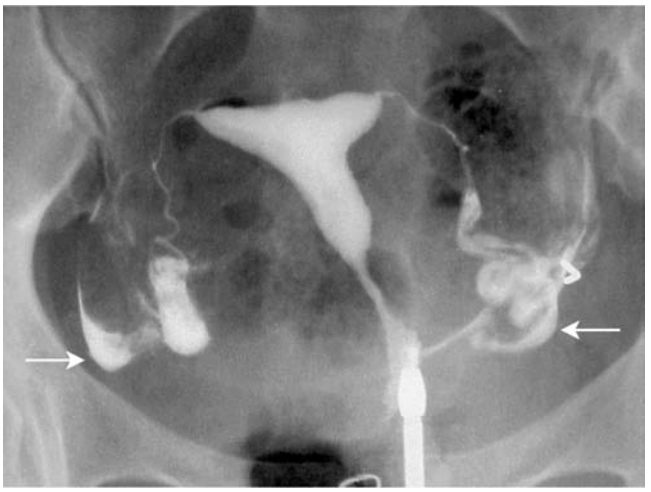

Figure 3.5 Normal HSG. This HSG demonstrates a uterine cavity that has a normal shape, and there are no filling defects noted within the cavity. Both fallopian tubes have filled and the arrows point to the dye that has exited the ends of both tubes into the abdominal cavity. *Abbreviation*: HSG, hysterosalpingogram.

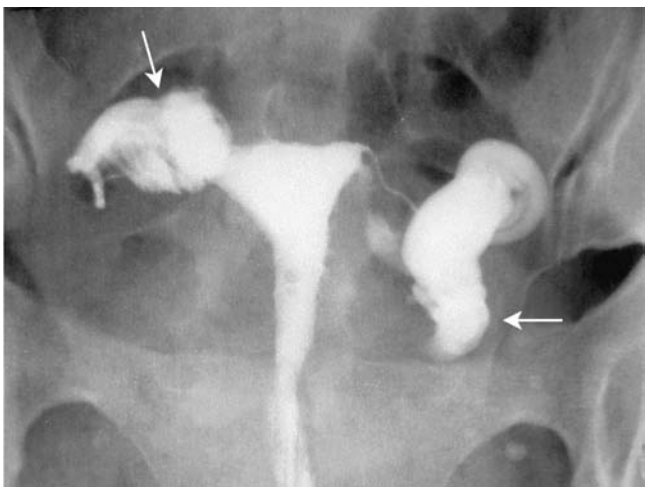

Figure 3.6 Distal tubal obstruction. In this X ray, both fallopian tubes are filled, but their distal ends are dilated and no dye is seen escaping into the abdominal cavity. The ends of the tubes are indicated by the arrows. This finding is most likely the result of a pelvic infection.

not go into the intravascular space. However, if the woman has a known iodine allergy, the test should be reconsidered. If the allergy is mild, the test can be performed with a contrast medium that contains nonionic iodine, which reduces the chance of an allergic reaction. If the woman has a more significant iodine allergy, the clinician should consult with the radiologist before performing the test. It may be recommended to pretreat the patient with steroids and/or antihistamines prior to the procedure. Another alternative is to use gadolinium contrast, which is used for MRI. Adequate visualization is appreciated with gadolinium but it is significantly more expensive than iodine contrast agents (21). It was previously thought that a fish allergy was synonymous with an iodine allergy, but this is not the case. Fish allergies are from a muscle protein and not related in anyway to iodine.

In addition to assessing tubal patency, the HSG allows examination of the uterine cavity (Figs. 3.7–3.13). If a balloon catheter is used for the HSG, the balloon should be deflated at the end of the contrast injection to better visualize the endometrial cavity. We routinely attach a tenaculum to the anterior cervix for traction and inject the dye through a cannula with a plastic cone-shaped tip that is abutted against the external cervical os. Retraction of the tenaculum

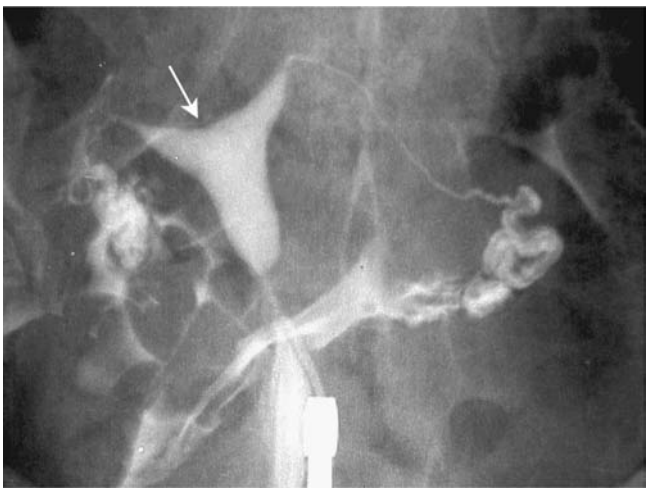

Figure 3.7 Arcuate uterus. In this otherwise normal study, a depression can be seen indenting the superior aspect of the uterine cavity (*arrow*). This is compatible with an arcuate uterus and is considered a normal variant. No additional workup is indicated. For comparison, a normal uterine cavity can be seen in Figures 3.5 and 3.6.

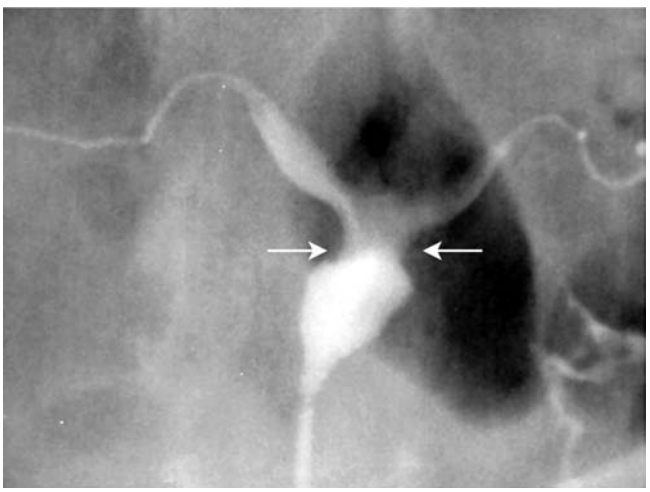

Figure 3.8 A DES uterus. The shape of this uterine cavity is compatible with previous DES exposure that causes impingement of the lateral walls as indicated by the arrows. The prominent uterine horns create a bicornuate shape as well. Overall, the uterine cavity has a "T shape" that is classic for previous DES exposure. *Abbreviation*: DES, diethylstilbestrol.

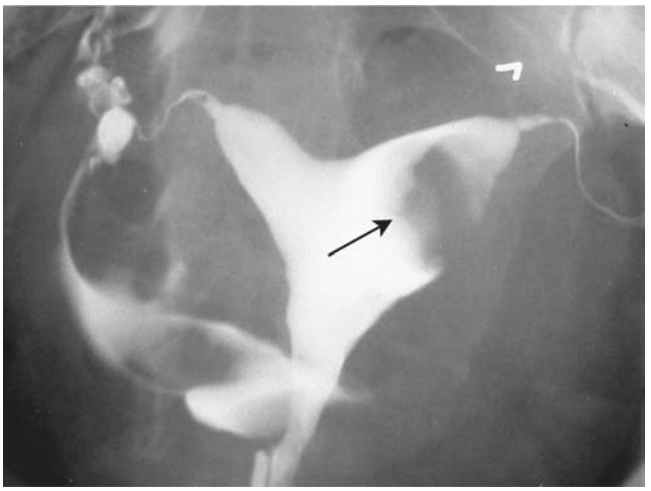

Figure 3.9 Submucosal fibroid. This hysterosalpingogram demonstrates a large filling defect in the left uterine horn, which was later found to be a submucosal fibroid. Also note the depression in the superior aspect of the cavity, which is an arcuate deformity.

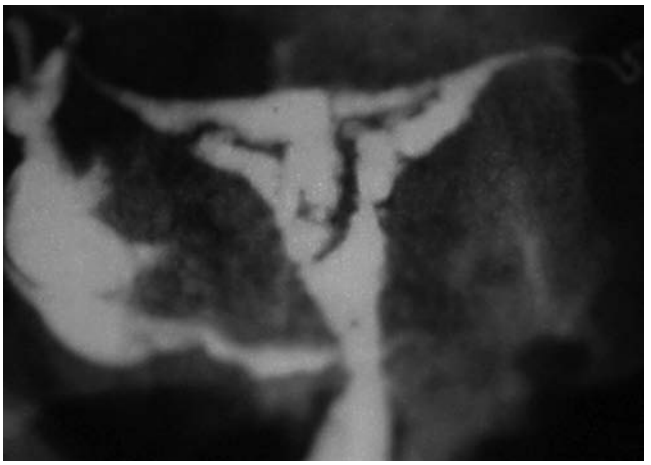

Figure 3.10 Asherman's syndrome. This HSG demonstrates multiple filling defects compatible with Asherman's syndrome. The patient is s/p D&C and underwent hysterscopic lysis of adhesions with restoration of the uterine cavity. *Abbreviation*: HSG, hysterosalpingogram.

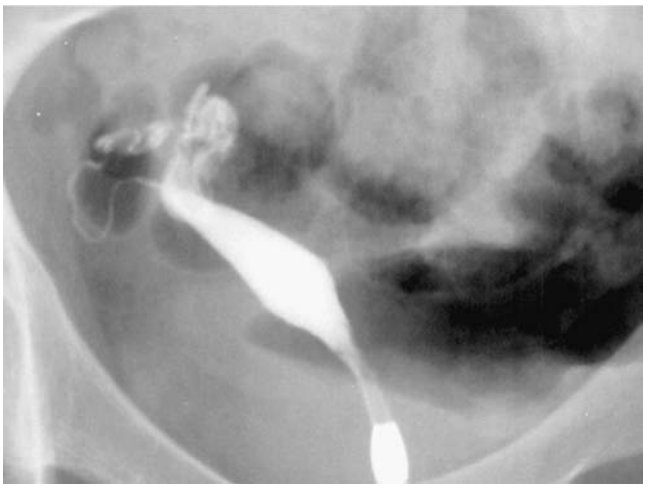

Figure 3.11 Unicornuate uterus. During this X ray, only the right horn of the uterine cavity filled. This is compatible with a unicornuate uterus. A unicornuate uterus increases the risk of premature labor and fetal malpresentations. It can be accompanied by renal abnormalities.

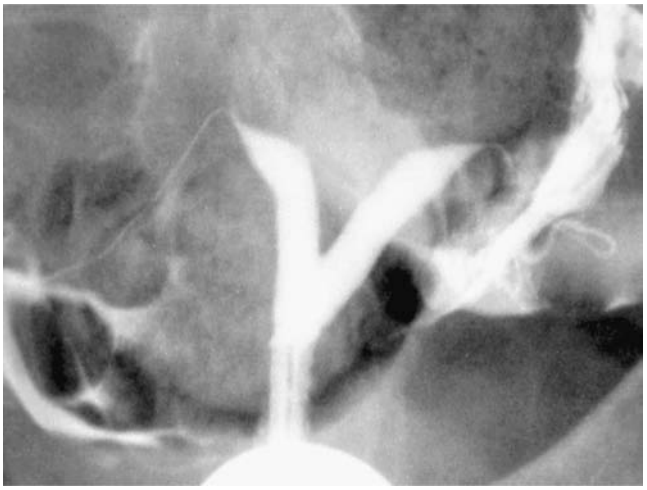

Figure 3.12 Uterine septum. This X ray demonstrates a division in the uterine cavity, which was confirmed to be a uterine septum.

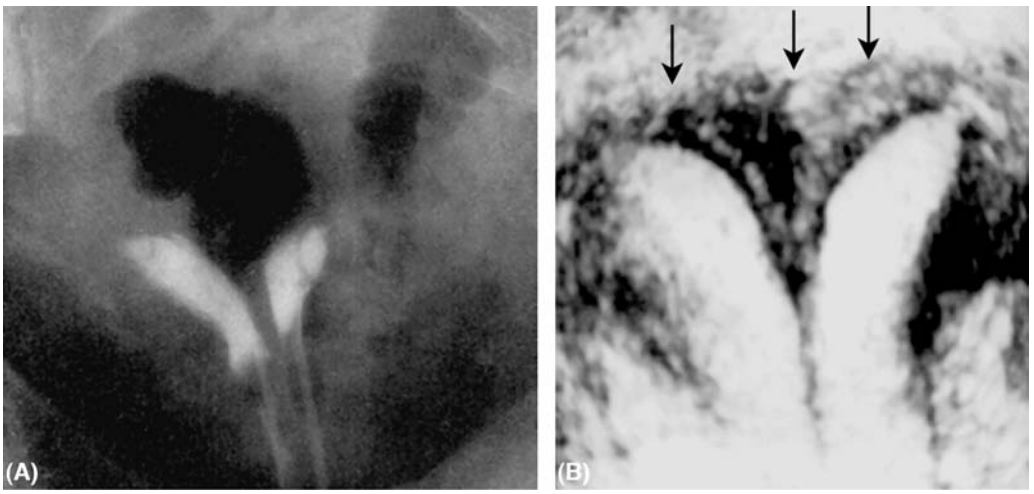

Figure 3.13 Is this uterine anomaly a septate or bicornuate uterus? Panel (**A**) shows a uterine duplication anomaly confirmed by an HSG. Two separate cervices were cannulated and two separate uterine horns were noted. Panel (**B**) shows a three-dimensional ultrasound image of the uterus of the same patient. The black arrows note the border of the outer extent of the myometrium of the uterine fundus. Conclusion: the anomaly is a uterine septum. *Abbreviation*: HSG, hysterosalpingogram.

caudad straightens out the uterus and allows a better examination of the cavity. If the dye is injected slowly and if a nonsteroidal anti-inflammatory drug (e.g., ibuprofen 600 mg) is given one hour prior to the procedure, the HSG can be performed with minimal discomfort and often painlessly contrary to popular belief.

Besides being a diagnostic tool, the HSG has been shown to be of therapeutic benefit as well. Approximately 30% of patients who have a normal HSG will conceive over the following six months (22,23). Initially, this was thought to be only a characteristic of the oil-based contrast medium. A prospective randomized study demonstrated comparable pregnancy rates over a six-month period in patients who had tubal patency confirmed using either a water-based or an oil-based contrast medium (22). In an effort to explain the therapeutic benefit of the HSG, some have suggested that the injection of dye may dislodge intratubal mucus plugs, stimulate the tubal cilia, or break up intratubal adhesions.

When Is a Laparoscopy Indicated?

A laparoscopy is the most invasive of the infertility tests and, for this reason, is generally performed in selected cases after the completion of the workup. In the past, it was considered a routine part of the infertility evaluation, but presently we counsel our patients on the risks and benefits of the procedure and perform it on an individual basis. There are some women who choose to have a laparoscopy during the initial part of the evaluation, while others choose never to have the surgery performed and proceed with treatment. A laparoscopy may be more seriously considered for the patient who has a history of a pelvic infection, signs or symptoms compatible with endometriosis, or abnormal findings on the HSG. It is important that the findings at the time of surgery are clearly documented not only with an accurate operative note but drawings, pictures, and video recordings are also helpful. At the time of the laparoscopy, the surgeon must have the necessary tools available to treat any conditions that are encountered. If endometriosis is identified, the patient should be properly staged. Staging sheets can be obtained by contacting the American Society of Reproductive Medicine in Birmingham, Alabama, or obtaining a copy of the article titled "Revised American Society for Reproductive Medicine classification of endometriosis" (24). There is no documented evidence that medical treatment of endometriosis enhances fertility. There continues to be uncertainty of the role of surgical treatment in cases of endometriosis to enhance fertility, mainly from the lack of well-controlled studies. This is the topic of a recent review (25). Another indication to perform a laparoscopy is when distal tubal obstruction is identified. If the patient cannot afford IVF, then correction of the obstruction (often covered by insurance companies) might be considered; but the patient should be counseled that the overall success rate is no higher than 20% forever. Alternatively, if the patient plans to undergo IVF treatment, then a salpingectomy should be performed since evidence suggests that a hydrosalpinx reduces the chance of pregnancy by 50% (26). The mechanism by which a hydrosalpinx reduces IVF implantation is likely related to the adverse affect of the tubal fluid on the endometrium or embryo.

Uterine Factor Infertility

Dysfunction in the uterus can prevent the establishment of a pregnancy. Further evaluation of the uterine cavity should be considered for any woman who has abnormal bleeding, an abnormal cavity noted on the HSG, or a history of repeated miscarriages. Uterine fibroids are a common finding and occur in approximately 15% to 20% of women over the age of 35. In the majority of cases, the fibroids do not produce symptoms or impact on fertility. Fibroids can be located and attached to the outside of the uterus (subserosal), in the uterine wall (intramural), and in the cavity (submucosal). It is the submucosal fibroids that can have the greatest impact on fertility. The management of uterine fibroids has changed dramatically over the years. In the past, it was standard to recommend that asymptomatic fibroids 2 cm or larger be removed. However, the approach has changed since there is a great deal of controversy concerning the role of fibroids on fertility and complicating pregnancy (27,28). Unfortunately, most published studies looking at the effectiveness of a myomectomy are retrospective in design and prospective randomized studies are lacking. Specific reasons to consider surgical removal of the fibroids include size (5 cm or larger), location within the cavity, association with menorrhagia, or distortion of the uterine cavity on the HSG.

The HSG provides a good examination of the cavity, but the examination can be somewhat limited. When the clinician is suspicious of an abnormality in the cavity, then further testing may be indicated with a diagnostic hysteroscopy or a sonohysterogram (SHG). We have found that the SHG is an excellent test to evaluate the cavity. This test can be performed in the office if the clinician has access to a vaginal ultrasound. To perform the test, a small catheter is inserted into the cavity and a syringe filled with saline is attached. Then the vaginal ultrasound is inserted. After the uterus is identified, saline is injected into the cavity. A normal cavity has sharp borders (Fig. 3.14). Any structure seen within the cavity is considered abnormal and could represent a polyp or fibroid (Fig. 3.15). Under this circumstance, a hysteroscopic examination would be indicated.

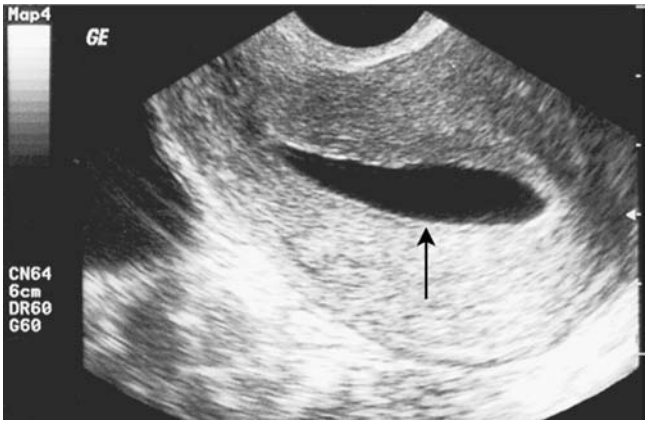

Figure 3.14 Sonohysterogram (normal cavity). This is a longitudinal image of the uterus taken at the time of a sonohysterogram. The black area (*arrow*) is the image of the saline that has been injected into the uterine cavity. Note that the borders of the uterine cavity are sharp and no masses are noted to be entering into the cavity. This study confirms a normal uterine cavity.

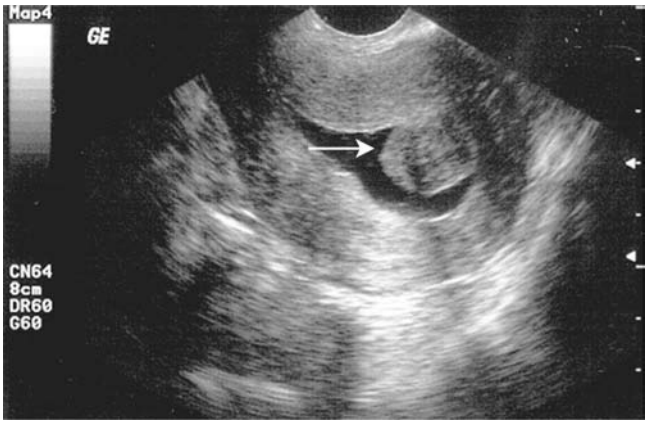

Figure 3.15 Sonohysterogram (abnormal cavity). In this image, the injected fluid in the cavity (*appearing black*) outlines an intracavitary mass, which was later confirmed to be a uterine fibroid.

CONCLUSIONS

The causes of infertility can be varied, and the infertility evaluation provides a better understanding of the potential causes. Up to 25% of couples will have a combination of factors. Therefore, it is important that a complete evaluation is performed and the evaluation is not halted after a single abnormal test is encountered. After the evaluation is completed, the couple should be seen in consultation to discuss the results and formulate a treatment plan.

REFERENCES

1. Hendriks DJ, Mol BWJ, Bancsi LF, et al. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. Fertil Steril 2005; 83:291–301.
2. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril 2011; 95:747–750.
3. Riggs RM, Hakan Duran E, Baker MW, et al. Assessment of ovarian reserve with anti-Müllerian hormone: a comparison of the predictive value of anti-Müllerian hormone, follicle-stimulating hormone, inhibin B and age. Am J Obstet Gynecol 2008; 199:202.e1–202.e8.
4. Fanchin R, de Ziegler D, Olivennes F, et al. Exogenous follicle stimulating hormone ovarian reserve test (EFFORT): a simple and reliable screening test for detecting 'poor responders' in in-vitro fertilization. Hum Reprod 1994; 9:1607–1611.

5. Abdalla H, Thum MY. An elevated basal FSH reflects a quantitative rather than a qualitative decline of the ovarian reserve. Hum Reprod 2004; 19:893–898.
6. Rossmanith WG, Laughlin GA, Mortola JF, et al. Pulsatile cosecretion of estradiol and progesterone by the midluteal phase corpus luteum: temporal link to luteinizing hormone pulses. J Clin Endocrinol Metab 1990; 70:990–995.
7. Coutifaris C, Mayers ER, Guzick DS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004; 82:1264–1272.
8. Shoup D, Mishell DR Jr, Lacarra M, et al. Correlation of endometrial maturation with four methods of estimating day of ovulation. Obstet Gynecol 1989; 73:88–92.
9. Li T-C, Dockery P, Rogers AW, et al. How precise is histologic dating of endometrium using the standard dating criteria? Fertil Steril 1989; 51:759–763.
10. Batista MC, Cartledge TP, Merino MJ, et al. Midluteal phase endometrial biopsy does not accurately predict luteal function. Fertil Steril 1993; 59:294–300.
11. Grimes DA. Validity of the postcoital test. Am J Obstet Gynecol 1995; 172:1327.
12. Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001; 345:1388–1393.
13. Tal R, Holland R, Belenky, et al. Incidental testicular tumors in infertile men. Fertil Steril 2004; 82:469–471.
14. Simon SD, Lee RD, Mulhall JP. Should all infertile males undergo urologic evaluation before assisted reproductive technologies? Two cases of testicular cancer presenting with infertility. Fertil Steril 2001; 75:1226–1227.
15. Nagler HM, Luntz, RK, Martinis FG. Varicocele. In: Lipshultz LI, Howards SS, eds. Infertility in the Male. St Louis, Mo: Mosby Year Book, 1997:336–359.
16. Evers JL, Collins JA. Surgery or embolization for varicocele in subfertile men. Cochrane Database Syst Rev 2005; (4).
17. DeBraekeleer M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod 1991; 6:245–250.
18. Pryor JL, Kent-First M, Muallem A, et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997; 336:534–539.
19. Pittaway DE, Winfield AC, Maxson W, et al. Prevention of acute pelvic inflammatory disease after hysterosalpingography: efficacy of doxycyline prophylaxis. Am J Obstet Gynecol 1983; 147:623–626.
20. The American College of Obstetricians and Gynecologist. Practice Bulletin No. 104: Antibiotic prophylaxis for gynecologic procedures. Obstet Gynecol 2009; 1–9.
21. Noorhasan D, Heard MJ. Gadolinium radiologic contrast is a useful alternative for hysterosalpingography in patients with iodine allergy. Fertil Steril 2005; 84:1744.e5–1744.e6.
22. Alper MM, Garner PR, Spence JE, et al. Pregnancy rates after hysterosalpingography with oil- and water-soluble contrast media. Obstet Gynecol 1986; 68:6–9.
23. Schwabe MG, Shapiro SS, Haning RV. Hysterosalpingography with oil contrast medium enhances fertility in patients with infertility of unknown etiology. Fertil Steril 1983; 40:604–606.
24. American Society for Reproductive Medicine classification of endometriosis 1996. Fertil Steril 1997; 67:817–821.
25. Vercellini P, Somigliana E, Vagano P, et al. Surgery for endometriosis-associated infertility: a pragmatic approach. Hum Reprod 2009; 24:254–269.
26. The Practice Committee of the American Society for Reproductive Medicine. Salpingectomy for hydrosalpinx prior to in vitro fertilization. Fertil Steril 2004; 82:S117–S119.
27. Hurst BS, Matthews ML, Marshburn PB. Laparoscopic myomectomy for symptomatic uterine myomas. Fertil Steril 2005; 83:1–23.
28. The Practice Committee of the American Society for Reproductive Medicine Educational Bulletin. Myomas and reproductive function, 2001.

4 Preconceptional counseling

Steven R Bayer

The goal of treatment of the infertile woman goes beyond just simply helping her achieve a pregnancy, but rather the ultimate goal is the establishment of a pregnancy that ends with a healthy mother and a healthy baby. An important prerequisite to infertility treatment is preconceptional counseling. Preconceptional counseling is an assessment of the medical, social, genetic, environmental, and occupational factors that can impact on fertility and the health of a pregnancy (Fig. 4.1). In this chapter, a comprehensive summary and framework for preconceptional care is presented.

LIFESTYLE HABITS

A social history with an assessment of lifestyle habits is an important part of the medical history that should be obtained from the male and female partners. The use of tobacco, alcohol, and recreational drugs should be ascertained and the couples appropriately counseled. These habits may not only be harmful during pregnancy but could also impair conception.

Smoking

Smoking is one of the major public health care issues which continues to challenge the medical community. According to the Center for Disease Control and Prevention (CDC), there is an encouraging downward trend of smoking in the United States from 24.1% to 20.6% between 1998 and 2008. Approximately 18% of women in the reproductive age group continue smoke (1). The ill effects of smoking on general health are well known. There are substantial data to support that smoking compromises reproductive health and is considered a reproductive toxin (2). Women who smoke are at greater risk of having infertility, a spontaneous abortion, and a tubal pregnancy. During pregnancy, maternal smoking increases the chances of abruptio placenta, premature rupture of the membranes, and impaired fetal growth. Maternal smoking during pregnancy also increases the chance of the sudden infant death syndrome (SIDS). Smoking may also be mutagenic causing damage to DNA and chromosomes. Maternal smoking increases the risk of trisomy 21 (3,4). It is clear that any woman who smokes and is contemplating a pregnancy should be strongly encouraged to stop smoking. It is encouraging that 70% of active smokers would like to stop but nicotine is a strong addiction and simple counseling will not prove effective in most cases. Referring the patient back to her primary care physician is prudent for counseling and intervention. Strategies for smoking cessation include behavioral modification, over-the-counter nicotine replacement products, and pharmacologic agents including bupropion and varenicline tartrate. The CDC has been very active in smoking cessation, and for additional information visit their Web site: http://www.cdc.gov/tobacco/osh/index.htm.

Alcohol

Alcohol use during pregnancy increases the risk of several complications and the most concerning complication is "fetal alcohol syndrome," which is associated with altered fetal growth, dysmorphic features, and mental retardation. The risk of fetal alcohol syndrome is related to the degree and timing of alcohol intake but no level of alcohol intake is considered safe. Previous studies have demonstrated that maternal alcohol intake can decrease the chances of conception (5,6). Therefore, any woman who is trying for a pregnancy should limit alcohol intake and avoid it altogether once pregnancy is established. Finally, heavy alcohol intake may suggest an addiction and a history of other drug use should be ascertained. In some cases, referral for counseling may be indicated before the couple attempts a pregnancy.

Recreational Drug Use

The use of recreational drugs is absolutely contraindicated while a couple is attempting to conceive and during pregnancy. Males who use marijuana on a regular basis have lower serum

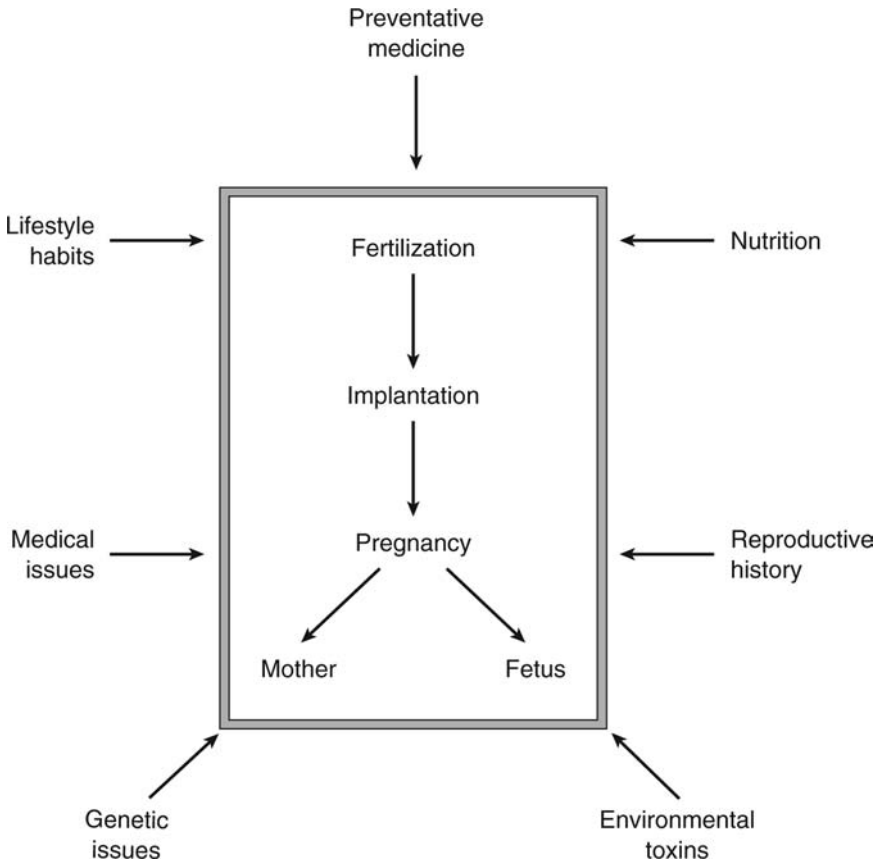

Figure 4.1 Factors that can impact on fertility and pregnancy.

testosterone levels and decreased sperm counts. Other drugs used by the mother, such as cocaine and heroin, may lead to a severe neonatal withdrawal reaction. Further, the use of intravenous drugs increases the risk of human immunodeficiency virus (HIV) and hepatitis infections.

BODY WEIGHT/NUTRITION

There is no doubt that our general health is influenced by what we eat, how much we eat, and how much energy we expend with activity and exercise. In addition, nutrition impacts on reproductive health can influence the establishment and maintenance of a pregnancy. There is growing concern about the increased incidence of obesity [body mass index (BMI) > 30] in the United States. There is evidence to suggest that we are in the midst of an epidemic of this problem. From 1988 to 2008, the incidence of obesity (BMI > 30) increased 1.5-fold from 22.9% to 33.8% and the incidence of extreme obesity (BMI > 40) increased twofold from 2.9% to 5.7% (7). In 2008, obesity affected 30% of the U.S. population or 100 million persons. The rate of obesity is also disparate among different ethnic populations. The rates of obesity in non-Hispanic white women, non-Hispanic black women, and Mexican-American women were 33%, 50%, and 45%, respectively. While there may be a genetic or medical explanation for some, the majority of cases of obesity are preventable and simply the result of a sedentary lifestyle and an unhealthy diet. If the trend does not change, obesity may become one of the leading causes of death.

A major concern about increased body weight is the increased incidence of complications that may occur during pregnancy including spontaneous abortion, gestational diabetes, hypertension, thromboembolism, congenital anomalies, and stillbirth (8,9). Women who are overweight tend to have babies with macrosomia, which increases the chance of shoulder

Table 4.1 Body Mass Index (BMI) Classifications

Weight classification	BMI
Underweight	<20
Normal	20–25
Overweight	25–30
Obesity	>30
Class I	30–35
Class II	35–40
Class III	>40

dystocia and the need for a cesarean section. A cesarean section that is performed on a woman who is overweight is associated with a higher incidence of anesthetic and surgical complications. Obesity is responsible for 18% of maternal mortalities and 80% of anesthesia-related mortalities (10). Guidelines have been published that provide a strategy for the clinician in dealing with obesity in the patient population (11,12).

In response to the growing obesity problem, the U.S. Department of Agriculture recently has revised the Food Guide Pyramid (http://www.mypyramid.gov/). The major differences in the current recommendations include reduced consumption of carbohydrates and increased physical activity. As a general recommendation, women should be encouraged to maintain a balanced diet of grains, vegetables, fruits, meats, and dairy products. Foods with a high content of fats and oils and carbohydrates should be used sparingly. In addition to a well-balanced diet, caloric intake should be limited to maintain a normal body weight. It is also recommended that one engages in aerobic exercise for 30 minutes a day.

Assessing the Body Habitus

The body mass index (BMI) or the Quetelet's index is a determination of whether an individual's weight is appropriate. It is a calculation that takes into account the weight and height (weight (kg)/height (m^2)). A reference table to calculate the BMI is provided. The BMI is a quantitative measure that helps to put into perspective the individual's weight (10).

Recommendation prior to conception:

- BMI > 30, refer to a nutritionist
- BMI > 35, refer to a high-risk obstetrician
- BMI > 40, defer treatment

Caffeine Intake

There have been several publications in the literature, which have suggested a dose-dependent relationship between caffeine intake and reduced fertility. Further, caffeine intake during pregnancy is associated with an increased chance of a spontaneous abortion and a low birth weight (13). Therefore, it is reasonable to suggest women who are attempting and during pregnancy to discontinue their caffeine intake altogether or at least limit their intake to one caffeinated beverage a day. The quantity of caffeine in beverages is variable. The average amount in a cup of coffee, tea, and a can of soda is approximately 100, 50, and 50 mg, respectively. Men experience no fertility risk from caffeine intake. Interestingly, sperm exposed to caffeine-like drugs in the laboratory actually have been shown to enhance motility.

Vitamin Supplementation

Women who take folic acid prior to pregnancy reduce their chance of having a baby with a neural tube defect. Neural tube defects are abnormal developments of the spine and skull. The most common types of neural tube defects are anencephaly and spina bifida. In the United States, the occurrence of neural tube defects is 1 to 2 per 1000 deliveries. Previous studies have reported that women who supplemented their daily diet with 0.4 mg of folic acid experienced a 40% to 100% reduction in the frequency of neural tube defects (14–17). Some studies have suggested that folic acid may prevent the development of other birth defects including cardiac, renal, cleft lip/palate, and limb abnormalities (18,19). It is now recommended that all women

of childbearing age who are capable of becoming pregnant should consume 0.4 mg of folic acid per day. This can be accomplished either through dietary supplementation or by taking an over-the-counter multivitamin preparation, which contains 0.4 mg of folic acid.

Women who are overweight (BMI > 30) have an increased chance of having a baby with a neural tube defect (9,20). In this population, it is prudent to prescribe a daily supplement of 1.0 mg of folic acid or a prenatal vitamin, which also contains 1.0 mg of folic acid (Box 1). It is recommended that a woman who has had a previous pregnancy complicated by a neural tube defect or a family history of this defect should be treated with 4.0 mg of folic acid daily (21–23).

Box 1 Recommendations for folic acid supplementation to prevent neural tube defects (NTDs)[a]

Routine: 0.4 mg daily (a multivitamin)
Obesity (BMI > 30): 1.0 mg daily (a prenatal vitamin or a 1.0-mg folic acid tablet)
Previous history or family history of NTD: 4.0-mg folic acid daily[b]

[a]For adequate prevention of an NTD, the folic acid supplement should be started one month before conception and continued during pregnancy.
[b]This level of intake can be achieved either by taking four 1.0-mg tablets of folic acid or three 1.0-mg folic acid tablets plus a prenatal vitamin. To achieve this level of supplementation, more than one multivitamin (or prenatal vitamin) should *not* be taken on a daily basis. This will increase the intake of vitamin A over the safe level, which could increase the chances of birth defects.

While vitamin supplementation is helpful, excessive vitamin intake can prove to be harmful to the developing fetus. Published data have confirmed that excessive intake of vitamin A increases the chance of congenital anomalies involving craniofacial, cardiac, thymus, and central nervous system organ systems (24). Isotretinoin (Accutane®), a derivative of vitamin A, is used to treat severe acne. Women who take this drug orally during pregnancy have a 25% chance of congenital anomalies (25). Prenatal vitamins and over-the-counter multivitamins contain 5000 to 8000 IU of vitamin A, which is a safe dose. However, daily intake of vitamin A should not exceed 10,000 IU. Excessive intake of animal liver, a food that is rich in vitamin A, should also be avoided. Supplementation with β-carotene, a precursor of vitamin A, is not associated with a toxic effect.

Herbal Remedies

Over the past several years, there has been an increase in the use of alternative medical therapies including herbal remedies. Herbal remedies are advertised as "natural" but many have strong medicinal qualities. However, one must exercise caution in their use since there are very few published studies analyzing the effectiveness and safety of these agents especially during pregnancy (26). In a previous study, three commonly used herbs including St John's Wort, *Echinacea purpurea*, and *Ginkgo biloba* were demonstrated to be detrimental to egg and sperm function (27). It is important to ask patients about the use of all medications, including herbal remedies. Many patients do not view herbal or over-the-counter medications as "true" medications. Until published studies confirm the safety of herbal remedies, women should be encouraged to discontinue these agents before and after pregnancy is established.

GYNECOLOGICAL CARE

Every woman should have a yearly blood pressure check, physical examination, pelvic examination, and a Pap smear. The American College of Obstetricians and Gynecologists (ACOG) recommendations regarding the frequency of Pap smear screening is as follows:

- **Women in their twenties** should have a Pap smear every two years (assuming prior Pap smears have been normal).
- **Women age 30 and older** who have had three consecutive normal Pap smears should have a Pap smear every three years.

ACOG also recommends routine mammograms every one to two years between the ages of 40 and 49 and every year thereafter. Earlier screening may be indicated if there is a family history of breast cancer.

LABORATORY TESTING

Routine laboratory studies are an essential part of preconceptional care. In essence, the same tests that are routine for any pregnant woman should also be performed on the woman who is contemplating a pregnancy. The tests that we recommend are presented below (Box 2). A complete blood count (CBC) may identify a woman who has anemia or some other abnormality that needs attention. A blood type and screen may uncover the presence of an antibody that could increase the chance of isoimmunization. In addition, knowledge of the blood type is also advantageous when a patient is experiencing bleeding during the early part of pregnancy and the clinician needs to know whether anti-D immunoglobulin (RhoGAM) is indicated.

Box 2 Preconceptional blood work

TSH
CBC
Blood type and screen
Rapid plasma reagin (RPR)
Antibody screens for:
- Rubella
- Varicella
- Hepatitis: Hep B Antigen, Hep C Antibody
- HIV

Genetic screening (if indicated)

Thyroid function should be assessed with a serum thyroid-stimulating hormone (TSH) determination. Thyroid dysfunction is present in 3% to 10% of women. Since thyroid disorders can be genetic, any woman who has a family history of thyroid dysfunction should be screened with a TSH level along with thyroid peroxidase antibodies. Despite a normal TSH level, if a woman has positive thyroid antibodies, she is at risk for thyroid dysfunction in the future especially during pregnancy. Borderline hypothyroidism during the early stage of pregnancy has been reported to impact on fetal neuropsychological development (28,29). A previous study confirmed that 85% of patients receiving treatment for hypothyroidism required an increase in thyroid replacement during the first trimester of pregnancy, so close vigilance is indicated (30). During the postpartum period, thyroid antibodies can further alter thyroid function and place the woman at increased risk of postpartum depression. There is a great deal of controversy as to what is the upper limit of normal for the TSH level. Many laboratories use 4.0 to 5.0 mIU/L as the upper limit of normal, but many medical endocrinologists consider 2.5 mIU/L to be the upper limits of normal since 95% of women will have a TSH level between 0.4 and 2.5 mIU/L. The Endocrine Society has taken the position that a normal TSH level should be <2.5 mIU/L, whereas the position of the American Association of Clinical Endocrinologist (AACE) is that the upper limit of normal for the TSH level is 3.0 mIU/L. Still others feel that no treatment is needed as long as the TSH level is in the stated normal range for the laboratory, the patient is asymptomatic and has a normal free T4 level. It is our position that every woman with a TSH $>$ 4.0 be treated with thyroid supplementation but for those who fall in the range of 2.5 to 4.0—if the antiperoxidase antibodies are positive, then treatment is initiated, otherwise the patient can be followed with frequent TSH levels.

Certain infections during pregnancy can pose a health risk to the mother and/or fetus. During childhood, it is public policy to administer immunizations that provide protection against many of these infections. Despite these efforts, a segment of the population remains at risk because of failure to receive the vaccine or failure to convert to immunity following a vaccination. Determining the immune status to certain infections including rubella, varicella,

and hepatitis should be considered a routine part of preconceptional care. Screening for other infectious diseases may be indicated depending on the clinical circumstances.

Rubella (German Measles)

Rubella is a self-limited viral infection that is associated with a characteristic rash. A maternal infection during the first trimester of pregnancy can result in fetal death or cause severe damage to the fetal cardiac, neurological, ophthalmologic, and auditory organs. Since the introduction of the rubella vaccine in 1969, there has been a significant reduction in rubella infections and babies born with congenital rubella syndrome. However, one in nine women is not immune to rubella (31). Screening for rubella immune status should be routinely performed on any woman who is contemplating pregnancy. Those women who are nonimmune should be encouraged to receive the vaccine. The rubella vaccine is a live-attenuated virus, and the current CDC recommendations are that a woman should avoid pregnancy for one month after receiving the vaccine.

Varicella (Chicken Pox)

Varicella is a highly contagious viral infection that is caused by a herpes virus. Most individuals experience a memorable varicella infection during their childhood, which confers lifelong immunity. A nonimmune individual can acquire the infection after exposure to an individual who has a primary varicella infection or herpes zoster (a latent form of varicella). Symptoms of an infection include malaise, fever, and the development of characteristic vesicular lesions. Approximately 5% of individuals are nonimmune to varicella (32). There are concerns about a primary varicella infection that develops in an adult. Up to 20% of adults who acquire a primary varicella infection will develop a concomitant pneumonia, which is fatal in 40% of cases (33). If a pregnant woman develops the infection during the first trimester, there is an increased risk of congenital anomalies (32). Immunity to varicella can be assessed by blood testing for the presence of the varicella IgG antibody. A varicella vaccine is available and should be offered to nonimmune individuals. The vaccine is administered in two doses, four to eight weeks apart. It is recommended that pregnancy be avoided during the vaccination period and until one month after the last injection.

Hepatitis Screening

There are six types of viral hepatitis (A, B, C, D, E, and G). The severity and risk for vertical transmission varies depending on the type. Any woman who has been diagnosed with hepatitis in the past should receive counseling about the risks during pregnancy. Screening for hepatitis B and C is recommended for all pregnant women and those contemplating a pregnancy. While those with documented immunity to hepatitis pose no risk to the fetus, chronic carrier states do exist that can be associated with liver dysfunction and vertical transmission of the infection to the fetus. Women who have chronic active hepatitis should be appropriately counseled. Individuals who work with blood products or who are at high risk for a hepatitis B infection should be offered immunization. For additional information on this topic, the reader is referred to a recently published review (34).

HIV Testing

An HIV infection can lead to acquired immunodeficiency syndrome (AIDS). Many people who do not know that they are infected can infect others mainly through sexual contact. Of concern is that an asymptomatic woman who is infected with the virus can pass the infection to her unborn child. HIV testing should be performed on all couples trying to conceive. In the past, HIV was considered to be a contraindication to pregnancy because of vertical transmission. However, with the advent of highly active antiretroviral therapy (HAART) which involves the administration of three or more drugs, the risk of vertical transmission is $<1\%$ to 2%. Clearly, before any HIV-infected woman considers a future pregnancy, she should consult with an infectious disease expert and a maternal fetal medicine specialist.

MEDICAL HISTORY

An important aspect of preconceptional care is an in-depth medical history to identify medical problems that could complicate a pregnancy. A medical condition or the medications used to

treat the condition can have an impact on the establishment and health of a pregnancy. Another concern is that the pregnancy can worsen the medical condition and impact on the health of the mother. In some cases, obtaining medical clearance may be indicated from the treating physician or a high-risk obstetrician before initiating the treatment. Some of the more common medical problems that can be encountered are discussed below.

Diabetes Mellitus

Diabetes mellitus is a commonly encountered medical problem during pregnancy. It has been estimated that approximately 8.3% of the general population and between 2% and 5% of pregnant women have diabetes. Diabetes is associated with an increased incidence of congenital anomalies, which is directly related to the control of the diabetes prior to conception. A blood glucose level gives the clinician an idea of the glucose control at that point in time. The hemoglobin (Hgb) A1C level is an indicator of how well the diabetes has been controlled over the previous three to four months. If the HgbA1C is in the normal range (<6%), then the incidence of congenital anomalies approaches the incidence in the general population. In addition to the increased risk of congenital anomalies, poorly controlled diabetes during pregnancy is associated with increased fetal and maternal wastage. Therefore, the objective in the diabetic woman is to establish tight control of glucose levels prior to conception. Vascular disease can complicate diabetes and warrants an assessment of renal function and an ophthalmologic examination (to rule out a retinopathy) prior to pregnancy.

According to the American Diabetes Association's 2011 recommendations, screening for diabetes should be considered in **any woman who is overweight (BMI $\geq$25 kg/m^2) and has any one or more of the following factors:**

- Physical inactivity
- A first-degree relative with diabetes
- A high-risk race/ethnicity (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander)
- Women who delivered a baby >9lbs or have a history of gestational diabetes
- Hypertension
- High-density lipoprotein (HDL) cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Polycystic ovarian syndrome (PCOS)
- Severe obesity
- History of cardiovascular disease (CVD)
- Over the age of 45 years

Screening for diabetes can be accomplished by an HgbA1C, fasting plasma glucose test, or the 75-g oral glucose tolerance test (which includes a fasting plasma glucose test and a two-hour glucose determination). The American Diabetes Association interpretation of the testing tolerance test is given in Table 4.2. Patients diagnosed with diabetes should be referred for further evaluation and treatment.

Table 4.2 The 2011 American Diabetes Association (ADA) Threshold Glucose Values for a Two-hour Glucose Tolerance Test and HgbA1C Values

Test	Normal	Borderline	Diabetes
HgbA1C	$\leq$5.6%	5.7–6.4%	$\geq$6.5%
Fasting blood glucose[a]	<100 mg/dL	100–125 mg/dL	$\geq$126 mg/dL
2-hr blood glucose following an OGTT[b]	<140 mg/dL	140–199 mg/dL	$\geq$200 mg/dL

[a]Fasting is defined as no caloric intake for at least 8 hr.
[b]The oral glucose tolerance test (OGTT) involves a fasting blood glucose level, ingesting of 75 g anhydrous glucose dissolved in water, and then another blood glucose level 2 hr later.

Hypertension

Chronic hypertension is a commonly encountered medical problem and, if left untreated, can cause irreparable damage to the kidneys and heart. Women with chronic hypertension should have baseline renal studies performed prior to conceiving. Hypertension places a woman at increased risk of superimposed preeclampsia during pregnancy, even if it is well controlled. Presently, there are many types of medications that control hypertension. All medications should be investigated to assess whether there are any adverse effects on the fetus. As a general guideline, methyldopa and labetalol are considered safe to take during pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are contraindicated during pregnancy.

Celiac Disease

Celiac disease is an immune-mediated condition affecting the gastrointestinal (GI) tract. The symtomatology of the disease is brought on by the ingestion of gluten which is present in wheat, barley, and rye. This causes a chronic inflammatory process resulting in atrophy of the intestinal villi, which then causes malabsorption. Celiac disease affects 1% of the population and has a genetic component. It is more prevalent in those with other autoimmune disorders including type I diabetes and thyroiditis. Classic symptoms include constipation, diarrhea, abdominal pain, anorexia, and vomiting. However, other cases of celiac disease do not have any of the GI manifestations. A presenting symptom of celiac disease can be iron deficiency anemia. It also has been associated with infertility and recurrent miscarriages. In a recent publication by Kumar et al., the prevalence of celiac disease in a group of patients with unexplained infertility was 5.65% compared to 1.30% in the control group (35).

The recommended screening for celiac disease includes the IgA antihuman tissue transglutaminase (TTG) and IgA endomysial antibody immunofluorescence (EMA). If these tests are positive, then an endoscopy with biopsy of the second portion of the duodenum or beyond should be performed. If the biopsies confirm atrophy of the villi, then the diagnosis is confirmed. The recommended treatment is elimination of all gluten from the diet.

Advanced Maternal Age

Current technology has increased the ability for women well over the age of 40 years to achieve a pregnancy with egg donation. However, older women are at increased risk for complications during pregnancy as compared to their younger counterparts. With advancing age, every woman is at increased risk of developing diabetes mellitus, chronic hypertension, and coronary artery disease, which can complicate a pregnancy. Therefore, it is prudent that every woman over the age of 40 undergo a medical evaluation prior to undergoing treatment to assess her medical fitness for a pregnancy.

Medication Use

All medications that a woman is taking should be investigated for potential detrimental effects on a pregnancy. The Food and Drug Administration (FDA) has placed medications into several categories based on animal and human studies that have investigated the harmful effects of medications during pregnancy (see the FDA Drug Categories table on page 43).

It is clear that if a pregnant woman is taking a category X medication, then it should be discontinued. However, if a medication falls into one of the other categories, continuation of the medication during pregnancy may be considered if the benefits outweigh the risks. Consultation with a specialist is important and the decision to continue the medication is dependent on several factors. If the medical condition is not life threatening or of significant importance, then serious consideration should be given to discontinuing the medication. In other situations, not treating the medical condition may put the mother or fetus at risk. In this situation, the clinician must try to select a medication that is effective in treating the condition and yet minimizes the risk to the fetus. For any medical therapy, if the benefits of treating the medical condition clearly outweigh the risks to the fetus, then the medication should be continued.

There are several resources to find information about the safety of any medication during pregnancy. The Physician's Desk Reference (PDR) is a good resource. Pharmacists have

FDA Drug Categories for Fetal Toxicity

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

access to information that may be helpful. In addition, there are several internet resources including:

Reprotox® database available through Micromedex: http://www.micromedex.com
Teratogen Information System (TERIS): http://depts.washington.edu/terisweb/teris
Organization of Teratology Information Specialists (OTIS): www.otispregnancy.org

REPRODUCTIVE HISTORY

A reproductive history is an important part of preconceptional care and the details of previous pregnancies should be obtained. If a woman has had a previous pregnancy with complications, she could be at increased risk for the recurrence of these complications with a future pregnancy. Therefore, any pregnancy with an abnormal outcome should be investigated before attempting pregnancy. The correction of an underlying problem may improve the outcome of a future pregnancy. Some of the more common issues concerning the reproductive history are discussed below.

Recurrent Miscarriages

If a couple has experienced two or more miscarriages, then an evaluation is indicated. A survey of lifestyle issues and environmental factors may give insight into the pregnancy losses. The workup includes serum karyotypes on both the female and the male partner to rule out chromosomal anomalies. A balanced translocation can be present in up to 6% to 8% of couples. A menstrual history is important to determine whether ovulatory dysfunction may be a contributing factor. The female partner should have an assessment of TSH level, glucose, lupus anticoagulant, and anticardiolipin antibodies. An assessment of the uterine cavity should also be performed to rule out an anatomical reason for the pregnancy losses such as uterine fibroids, Müllerian defects, and diethylstilbestrol (DES) changes. An examination of the uterine cavity can be accomplished by a hysterosalpingogram, sonohysterogram, or a hysteroscopy.

Previous Stillborn or Infant Born with Congenital Anomalies

In most cases, when a previous pregnancy has resulted in a stillbirth or a baby with birth defects, testing is performed on the fetus and the couple undergoes counseling. However, if there is uncertainty about the depth or scope of the workup, then the couple should be referred to a high-risk obstetrician for a consultation to determine the risk with a future pregnancy.

History of Premature Labor

The causes of premature labor are varied and can be secondary to premature rupture of the membranes, an abnormal uterine cavity (secondary to uterine fibroids, a Müllerian defect, and

in utero DES exposure), chorioamnionitis, or an incompetent cervix. A history of premature labor places a woman at increased risk of a similar occurrence with a future pregnancy. A pregnancy complicated with premature labor and a malpresentation increases the likelihood of an underlying Müllerian anomaly, which has an incidence of 2% to 3% in the general population. A vaginal ultrasound and a hysterosalpingogram will help to determine whether there has been any abnormal development of the cavity. Painless dilatation prior to the delivery suggests the diagnosis of incompetent cervix. These women should be counseled on the benefits of a cervical cerclage with a future pregnancy. Finally, a multiple pregnancy should be avoided in women with a previous history of premature labor.

Gestational Diabetes

A woman who has been diagnosed with gestational diabetes during a pregnancy is at increased risk of recurrence during a future pregnancy. In addition, these women are at increased risk of developing adult onset diabetes during their lifetime (approximately 2% to 4% chance per year). For this reason, women with a history of gestational diabetes should be screened for glucose intolerance with an HgbA1C, fasting blood glucose, or a two-hour glucose tolerance test. If diabetes is diagnosed, then referral to a medical endocrinologist or a high-risk obstetrician would be in order prior to attempting pregnancy. Adequate control of diabetes before conception decreases the chance of congenital anomalies and complications during the pregnancy.

Severe Preeclampsia

Preeclampsia complicates 6% to 8% of all pregnancies. In most cases, preeclampsia occurs during the first pregnancy and does not recur. However, severe preeclampsia with onset during the second trimester may recur in 10% to 15% of future pregnancies. It may be increased to a greater degree if there are any underlying risk factors including diabetes, renal dysfunction, chronic hypertension, or a thrombophilia. Women with a history of severe preeclampsia may benefit from a referral to a high-risk obstetrician for counseling.

OCCUPATIONAL HISTORY

There is increased awareness about the impact of environmental toxic exposures on general and reproductive health. Toxic exposures at the workplace can put some individuals at considerable risk. The Occupational Safety and Health Administration (OSHA), a federal agency of the Department of Labor, was established in 1970 and has monitored safety in the workplace. One of the three categories of hazardous substances monitored by the OSHA is reproductive toxins. Reproductive toxins are categorized as mutagens, teratogens, fertility toxins, and toxins transferred at lactation. It has been estimated that 17% of working women are exposed to known teratogens in the workplace (36). The following is a discussion of some occupational risks that may pose a risk to reproduction.

Exposure to Anesthetic Gases

It is well documented that women who are exposed to anesthetic gases (i.e., operating room personnel, dental hygienists) are at increased risk for infertility, spontaneous abortion, and congenital anomalies (37–39). Of interest is that paternal exposure may also be of consequence. Women who were impregnated by men who were exposed to anesthetic gases were found to be at greater risk of a having a pregnancy complicated by a spontaneous abortion and congenital anomalies (38).

Exposure to Beauty Salon Chemicals

Beauty salon workers work in a complex environment and are exposed to many chemicals in hair dyes, permanent solutions, and bleaches. Furthermore, nail sculpturing also involves exposure to volatile chemicals that can be inhaled. A previous study concluded that beauty salon workers have an increased risk of miscarriage and infertility (40). The risk was influenced by the number of hours worked per week, the use of formaldehyde disinfectants, and the practice of using gloves during hair treatments and whether nail sculpturing was done in the salon.

Exposure to Video Display Terminals

Many jobs require long hours in front of a video display terminal (VDT), or computer monitor. The theoretical concern over a VDT is that it creates an electromagnetic field. It is reassuring that studies have failed to associate VDT exposure with an increased risk of a spontaneous abortion and infertility (41,42).

Organic Solvents

All women should be asked about exposure to organic solvents. Organic solvents include aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene, vinyl chloride, and acetone. Women at greatest risk for exposure to these chemicals are those who work in the health care profession, and the clothing and textile industries. However, women in other professions may be unknowingly exposed to these agents as well. In a previous prospective study, women who were exposed to organic solvents during the first trimester were followed throughout the pregnancy (43). When compared to a control group, there was no statistical difference in the rate of a spontaneous abortion and minor malformations. However, the group exposed to organic solvents had a statistically higher incidence of major malformations when compared to controls (12% vs. 1%, $p < 0.001$).

Exposure to Spermatotoxins

From a fertility standpoint, males are more susceptible to toxins since sperm production is an ongoing process. The first report of an occupationally related spermatotoxin appeared in the mid-1970s (44). It showed that men who worked at factories that produced dibromochloropropane (DBCP; a pesticide) had an increased incidence of infertility—the severity being dependent on the dose and length of exposure. Since this report was released, other spermatotoxins have been discovered including kepone, ethylene glycol ethers, carbon disulfide, naphthyl methylcarbamate, ethylene dibromide, organic solvents, and lead.

Recommendation

As part of preconceptional care, it is important to assess whether either the male or the female partner is exposed to any toxin in the workplace that may prove detrimental. All employers must provide material safety data sheets (MSDS) of all chemicals that are present in the workplace. Any potential risk is dependent on the specific toxin, length of time of exposure, and degree of exposure. If there is concern about an exposure, a consultation with a specialist in occupational medicine will help to clarify the risk.

GENETIC COUNSELING AND SCREENING

As our knowledge in the field of genetics grows, increased responsibility will rest with those who counsel and prepare couples for pregnancy. A genetic history should be part of every evaluation of the infertile couple. There is no consensus as to the scope and breadth of the genetic history. Ideally, every couple contemplating pregnancy would be evaluated by a geneticist or genetic counselor to determine their genetic risks. This obviously is not practical but a thorough assessment of genetic risk and counseling is indicated.

It is important that any practitioner who is providing genetic counseling has an understanding of the disease process, its inheritance, and the limitations of the screening tests that are currently available. In addition, it is of utmost importance that the clinician stays abreast of new clinical developments and screening tests that become available. In some cases, referral to a genetic counselor is indicated. Recommendations for genetic counseling and position statements concerning testing have been published by the American College of Obstetrics and Gynecology (http://www.acog.com) and the American College of Medical Genetics (http://www.acmg.net). An overview of some of the more common genetics issues follows.

Ancestral Backgrounds

An important aspect of the genetic history is an exploration of the ancestral backgrounds of both partners. Historically, individuals of a specific ethnic population are more likely to reproduce with others from the same population. This gives an opportunity for the

Table 4.3 Genetic Testing Based on Ancestral Backgrounds

Ancestral group	Disease	Screening test
Caucasian, Native American	Cystic fibrosis[a]	DNA testing
French Canadian, Cajun	Tay–Sachs	Assessment of hexosaminidase enzyme activity and DNA testing
Jewish[b]	Canavan disease	DNA testing
	Cystic fibrosis[a]	DNA testing
	Familial dysautonomia	DNA testing
	Tay–Sachs	Hexosaminadase enzyme activity and DNA testing
African, Asian, Cambodia, Caribbean, Central America, India, Indonesia, Laos, Malaysia, Mediterranean, Middle Eastern, Pakistan, Thailand, Turkey, Vietnam	Hemoglobinopathies	CBC, Hgb electrophoresis

[a]It is impractical to screen for all cystic fibrosis mutations since over 1000 mutations have been identified. Therefore, the clinician must realize the limitations of the screening and counsel couples accordingly. For instance, the detection rate of cystic fibrosis carriers in the Caucasian, Native American, and Jewish populations is 90%, 94%, and 97%, respectively.
[b]Recommendations from the American College of Obstetricians and Gynecologists (ACOG). Committee opinion; No. 442, October 2009.

propagation and higher prevalence rate of certain genetic disorders within these populations. Autosomal recessive diseases are most common. In this inheritance pattern, carriers are asymptomatic for the disease and both partners must be carriers to be at risk (1 in 4 chance) of having a child that could be affected by the disease. Some of the commonly inherited conditions and recommended testing is presented in Table 4.3. Many of these diseases can result in early death or significant morbidity. If an individual does not have an at-risk ancestral background but does have a family history of the disease, he/she should undergo screening. It is also important that any individual who is identified to be a carrier of a genetic disease should be instructed to tell his/her siblings so that they too can undergo screening.

Screening for Chromosomal Anomalies

In some situations, a chromosomal analysis may be indicated. The following are some indications in which a karyotype of the male and female partners may be indicated.

Recurrent Miscarriages

Couples with two or more miscarriages have a 5% to 8% chance of having a balanced translocation (45,46). This chromosomal abnormality may explain the repeated miscarriages. While this chromosomal abnormality may put a couple at risk for a miscarriage, the majority of gametes that are produced in affected individuals are chromosomally normal. If a viable pregnancy is established when one of the partners has a balanced translocation, there is concern that the fetus may have a chromosomal imbalance that would increase the risk of congenital anomalies. In these cases, the couple may consider genetic testing with chorionic villus sampling or a genetic amniocentesis.

History of Down's Syndrome

If a first-degree relative was diagnosed with Down's syndrome, then it should be ascertained whether that affected individual underwent chromosomal testing. Approximately 90% of cases of Down's syndrome are trisomy 21 which is a sporadic event. The remaining 10% are the result of a translocation. Of these, half are inherited and the other half occur de novo.

Therefore, if there is uncertainty about the etiology or the result of the chromosomal analysis of the affected individual with Down's syndrome, then a karyotype should be offered.

History of Stillbirth, Congenital Anomalies
In situations when a couple gives birth to a stillborn infant or an infant with a congenital anomaly, the chromosomal makeup of the fetus is usually tested. If this testing was not done or was inconclusive, then chromosomal testing of the couple should be offered.

Severe Male Factor Infertility
In males with azoospermia or severe oligospermia (<5 million sperm/cc), there is a 5% to 15% chance of chromosomal anomalies and 3% to 15% chance of microdeletions in the Y chromosome (47–49).

Fragile X Screening

Mental retardation can be caused by many factors including environmental, social, genetic, and unknown factors. The most commonly inherited type of mental retardation is Fragile X syndrome which affects 1 in 1200 males and 1 in 2500 females. Fragile X syndrome is the result of expansion of a repeat section on the long arm of the X chromosome. The degree of mental retardation can be borderline to severe and is related to the number of repeats within the mutation allele. Fragile X is associated with specific findings including a long thin face with prominent jaws, autistic features, and speech and language difficulties. Fragile X syndrome has an atypical inheritance. From one-third to one-half of females who carry the full mutation have Fragile X syndrome. If a woman is a carrier of a premutation, then she will not be affected by Fragile X syndrome but she is at increased risk of premature ovarian failure (prior to the age of 40). The premutation is identified in 2% and 14% of women with isolated and familial premature ovarian failure, respectively (50). Fragile X screening should be considered for couples with a family history of unexplained mental retardation, autism, or premature ovarian failure.

Maternal Age Counseling

Advanced maternal age is associated with an increased incidence of postfertilization chromosomal abnormalities in the embryo. This explains why increased maternal age is associated with an increased incidence of infertility, pregnancy loss, and fetal chromosomal abnormalities. While most pregnancies complicated by a chromosomal anomaly result in a miscarriage, others will progress to term resulting in a delivery. The incidence of fetal chromosomal abnormalities in relation to maternal age is shown in Table 4.4. Once pregnancy is achieved, the risk of a fetal chromosomal abnormality can be evaluated with quadruple serum screening of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), estriol and inhibin levels. For those at risk, prenatal genetic testing can be performed with a genetic amniocentesis or chorionic villus sampling.

Paternal Age Counseling

There is evidence that advanced paternal age can also pose a risk to the fetus. The increased incidence is not based on chromosomal abnormalities, but on the transmission of new genetic mutations. In contrast to oogenesis, spermatogenesis is an ongoing process that continues throughout a man's life beginning at puberty. The increased frequency of divisions within the spermatocytes increases the chance of errors that can result in a new mutation. These new mutations can result in the passage of an autosomal dominant disorder to an offspring or an X-linked recessive disorder to a grandson which is called the "grandfather effect." The incidence of the inheritance of an autosomal dominant condition is 1 in 5000 to 10,000 deliveries. While the paternal age effect on the occurrence of any specific autosomal dominant condition may be low, the combined effect on all autosomal dominant conditions can be significant. While

Table 4.4 Chromosomal Abnormalities in Liveborn Infants and Maternal Age[a]

Maternal age (yr)	Risk for Down's syndrome	Total risk for chromosomal anomalies[b]
20	1/1667	1/526
21	1/1667	1/526
22	1/1429	1/500
23	1/1429	1/500
24	1/1250	1/476
25	1/1250	1/476
26	1/1176	1/476
27	1/1111	1/455
28	1/1053	1/435
29	1/1000	1/417
30	1/952	1/385
31	1/909	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

[a]The data presented above were modified from Hook DB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249:2034–8, and Hook EB. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981; 58:282–5

[b]The other chromosomal anomalies that are increased with maternal age in addition to 47,+21 (Down's syndrome) are 47,+18; and 47,+13; 47,XYY (Klinefelter's syndrome); 47,XYY and 47,XXX. The incidence of 47,XXX for women between the ages of 20 and 32 years is not available

advanced paternal age increases the risk of these new mutations, testing for all these autosomal dominant and X-linked disorders is not possible. Further, there is no consensus as to the definition of advanced paternal age. It has been estimated that one-third of new autosomal dominant mutations are the result of advanced paternal age (>40). It seems prudent to suggest that men complete their families by age 40. Even though there is no easy way to screen for all these genetic conditions in utero, at the very least, couples should be made aware of the potential risk and given the opportunity to meet with a genetic counselor.

CONCLUSION

Any couple who is interested in pregnancy should have a thorough evaluation to identify factors that may put the patient at risk for a complicated pregnancy. Depending on the situation, further workup or counseling may be indicated before the couple attempts a pregnancy.

REFERENCES

1. CDC. Cigarette smoking among adults and trends in smoking cessation—United States, 2008. MMWR 2009; 58(44):1227–1232.
2. The Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility. Fertil Steril 2008; 90:S254–S259.
3. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update 2000; 6:122–131.
4. Yang Q, Sherman SL, Hassold TJ, et al. Risk factor for trisomy 21: maternal cigarette smoking and oral contraceptive use in a population-based case-control study. Genet Med 1999; 1:80–88.
5. Eggert J, Holger T, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. Fertil Steril 2004; 81:379–383.
6. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertil Steril 2003; 79:330–339.
7. Ogden CL, Carroll MD. Prevalence of overweight, obesity and extreme obesity among adults: United States, trends 1976–1980 through 2007–2008. Division of Health and Nutrition Examination Surveys. Available at: http://www.cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.pdf.
8. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009; 301:636–650.
9. Gunatilake RP, Perlow JH. Obesity and pregnancy: clinical management of the obese gravida. Am J Obstet Gynecol 2011; 204:106–119.
10. Endler GC, Mariona FG, Sokol RJ, et al. Anesthesia-related maternal mortality in Michigan, 1972–1984. Am J Obstet Gynecol 1988; 159:187–193.
11. The practical guide: identification, evaluation and treatment of overweight and obesity in adults. National Heart Lung and Blood Institute and North American Association for the study of obesity. Bethesda (MD); National Institutes of Health; 2000. Available at: www.nhlbi.nih.gov/guidelines/obesity/practgde.htm.
12. The American College of Obstetricians and Gynecologists. Obesity in pregnancy, 2005. Committee opinion; No. 315.
13. Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. Epidemiology 2004; 15:229–239.
14. Mulinare J, Cordero JF, Erickson JD, et al. Periconceptional use of multivitamins and the occurrence of NTDs. J Am Med Assoc 1988; 260:3141–3145.
15. Bower C, Stanley FJ. Dietary folate as a risk factor for NTDs: evidence from a case control study in Western Australia. Med J Aust 1989; 150:613–619.
16. Miles JL, Rhoads GG, Simpson JL, et al. The absence of a relationship between the periconceptional use of vitamins and NTDs. N Engl J Med 1989; 321:430–435.
17. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of NTDs. J Am Med Assoc 1989; 262:2847–2852.
18. Hall JG, Solehdin F. Folate and its various ramifications. Adv Pediatr 1998; 45:1–35.
19. McDonald SD, Ferguson S, Tam L, et al. The prevention of congenital anomalies with periconceptional folic acid supplementation. J Obstet Gynaecol Can 2003; 25:115–121.
20. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. J Am Med Assoc 1996; 275:1093–1096.
21. MRC Vitamin Study Research Group. Prevention of NTDs: results of the Medical Research Council Vitamin Study. Lancet 1991; 338:131.
22. Smithells RW, Nevin NC, Sellers MJ, et al. Further experience of vitamin supplementation for the prevention of NTD recurrences. Lancet 1983; 1:1027.
23. Vergel RG, Sanchez LR, Heredero BL, et al. Primary prevention of NTDs with folic acid supplementation: Cuban experience. Prenat Diagn 1990; 10:149.
24. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. N Engl J Med 1995; 333:1369–1373.
25. Lammer EJ, Hayes AM, Schunior A, et al. Unusually high risk for adverse outcomes of pregnancy following fetal isotretinoin exposure. Am J Hum Genet 1988; 43:A58.
26. Marcus DM, Snodgrass WR. Do no harm: avoidance of herbal medicines during pregnancy. Obstet Gynecol 2005; 105:1119–1122.
27. Ondrizek RR, Chan PJ, Patton WC, et al. An alternative medicine study of herbal effects on the penetration of zona-free hamster oocytes and the integrity of sperm deoxyribonucleic acid. Fertil Steril 1999; 71:517–522.

28. Morreale de Escobar G, Obregon MJ, Escobar del Rey F Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J Clin Endocrinol Metab 2000; 85:3975–3987.
29. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 342:549–555.
30. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004; 351:241–249.
31. Bayer SR, Turksoy RN, Emmi AM, et al. Rubella susceptibility of an infertile population. Fertil Steril 1991; 56:145–146.
32. Reid KC, Grizzard TA, Poland GA. Adult immunizations: recommendations for practice. Mayo Clin 1999; 74:377–384.
33. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med 1992; 13:679–691.
34. The Practice Committee of the American Society for Reproductive Medicine. Hepatitis and reproduction. Fertil Steril 2008; 90:S226–S235.
35. Kumar A, Meena M, Begum N, et al. Latent celiac disease in reproductive performance of women. Fertil Steril 2011; 95:922–927.
36. Makuc D, Lalich N. Employment characteristics of mothers during pregnancy. Health United States and Prevention Profile 1983. Washington, DC: US Government Printing Office; 1983:25–32. National Center for Health Statistics, DHSS publication (PHS) 841232.
37. Cohen EN, Bellville JW, Brown BW Jr. Anesthesia, pregnancy and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology 1971; 35:343–347.
38. Rowland AS, Baird DD, Weinberg CR, et al. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med 1992; 327:993–997.
39. Guirguis SS, Pelmear PL, Roy ML, et al. Health effects associated with exposure to anesthetic gases in Ontario hospital personnel. Br J Int Med 1990; 47:490–497.
40. John EM, Savitz DA, Shy DM. Spontaneous abortions among cosmetologists. Epidemiology 1994; 5:147–155.
41. Brent RL, Gordon WE, Bennett WR, et al. Reproductive and teratologic effects of electromagnetic fields. Reprod Toxicol 1993; 7:535–580.
42. Parazzini F, Luchini L, La Vecchia C, et al. Video display terminal use during pregnancy and reproductive outcome: a meta-analysis. J Epidemiol Community Health 1993; 47:265–268.
43. Khattak S, K-Moghtader G, McMartin K, et al. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. J Am Med Assoc 1999; 281:1106–1109.
44. Whorton D, Krauss RM, Marshall S, et al. Infertility in male pesticide workers. Lancet 1977; 2:1259–1261.
45. Plouffe L, White EW, Tho ST, et al. Etiological factors of recurrent abortion and subsequent reproductive performance of couples: have we made any progress in the past 10 years? Am J Obstet Gynecol 1992; 167:313.
46. Harger JH, Archer DF, Marchese SG, et al. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol 1983; 62:574.
47. DeBraekeler M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod 1991; 6:245–250.
48. Pryor JL, Kent-First M, Muallem A, et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997; 336:534–539.
49. Kent-First MG, Kol S, Muallem A, et al. The incidence and possible relevance of Y-linked microdeletions in babies born after intracytoplasmic sperm injection and their infertile fathers. Mol Hum Reprod 1996; 2:943–950.
50. Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Genet 2000; 97:189–194.

5 Clinical algorithms

Michael M Alper

This chapter contains clinical algorithms that will aid the physician in the day-to-day management of the infertile couple. Each infertile couple presents with a different set of circumstances, and the scope of the testing and recommended treatment will vary accordingly. The clinical algorithms are general guidelines regarding patient care, and other circumstances, including patient choice, may dictate a course of management other than that presented.

The following clinical algorithms are presented:

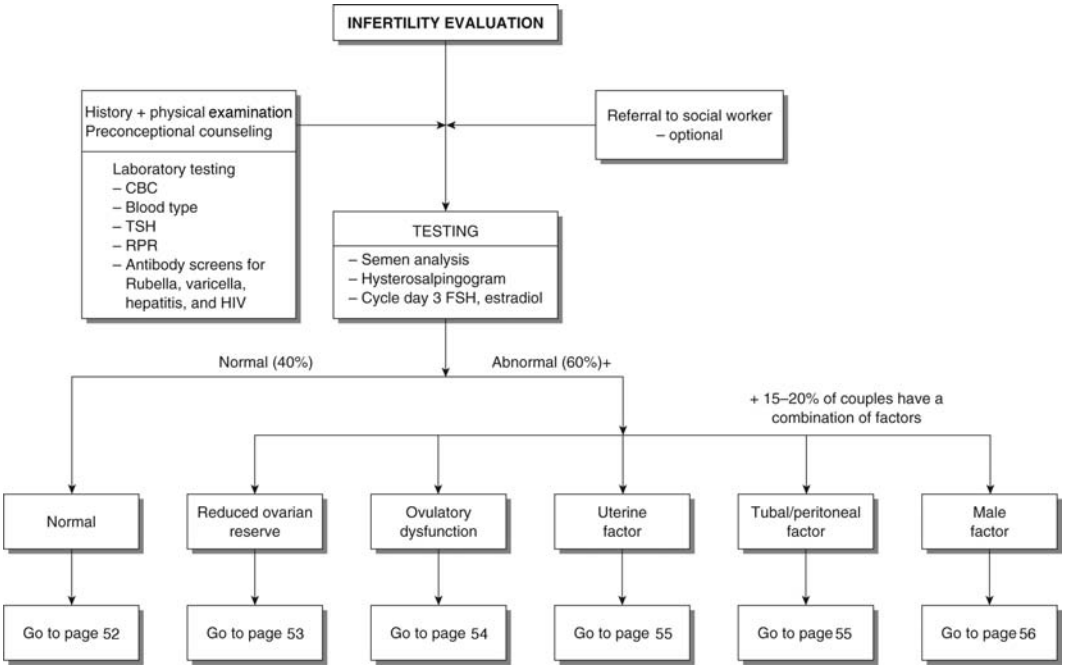

Figure 5.1 Infertility evaluation. *Abbreviations*: CBC, complete blood count; TSH, thyroid-stimulating hormone; RPR, rapid plasma regain; HIV, human immunodeficiency virus; FSH, follicle-stimulating hormone.

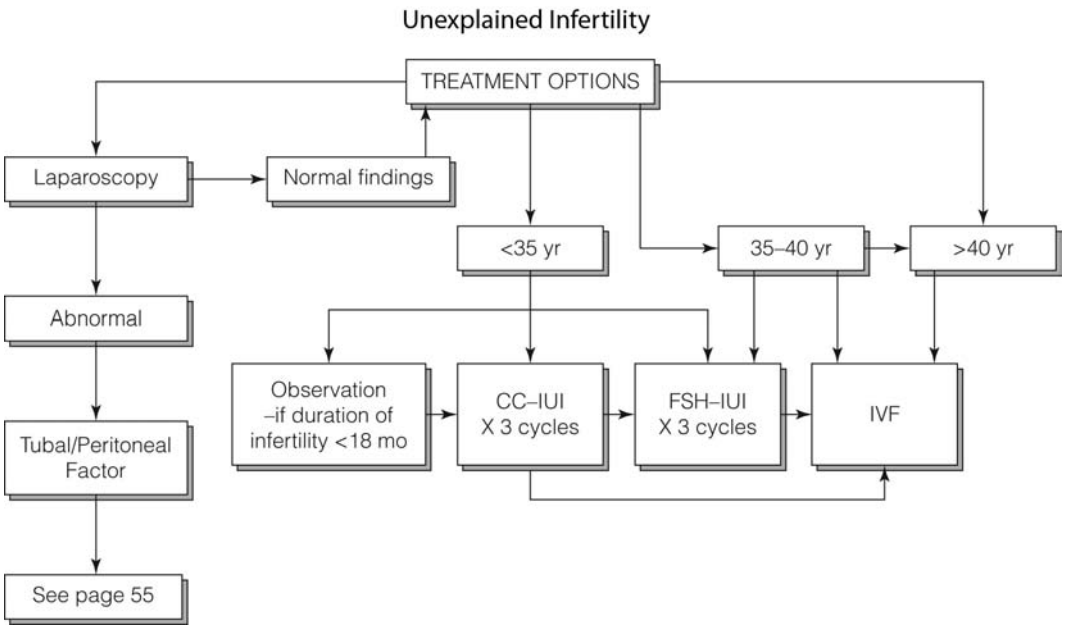

Figure 5.2 Unexplained infertility. *Abbreviations*: CC, clomiphene citrate; IUI, intrauterine inseminations; FSH, follicle-stimulating hormone; IVF, in vitro fertilization.

DIAGNOSIS:

The diagnosis of reduced ovarian reserve is supported by any of the following:

1. Cycle day 3 FSH $>$ 10 mIU/mL or eslradiol $>$ 70 pg/mL
2. Abnormal clomiphene challenge test

   To perform:

   - Cycle day 3 FSH, estradiol levels
   - Cloimphene citrate 100 mg cycle days 5–9
   - Cycle day 10 FSH level

   If any of the FSH levels are $>$ 10 mIU/mL or the estradiol is $>$ 70 pg/mL the test is considered abnormal
3. Documented poor response to aggressive ovulation induction

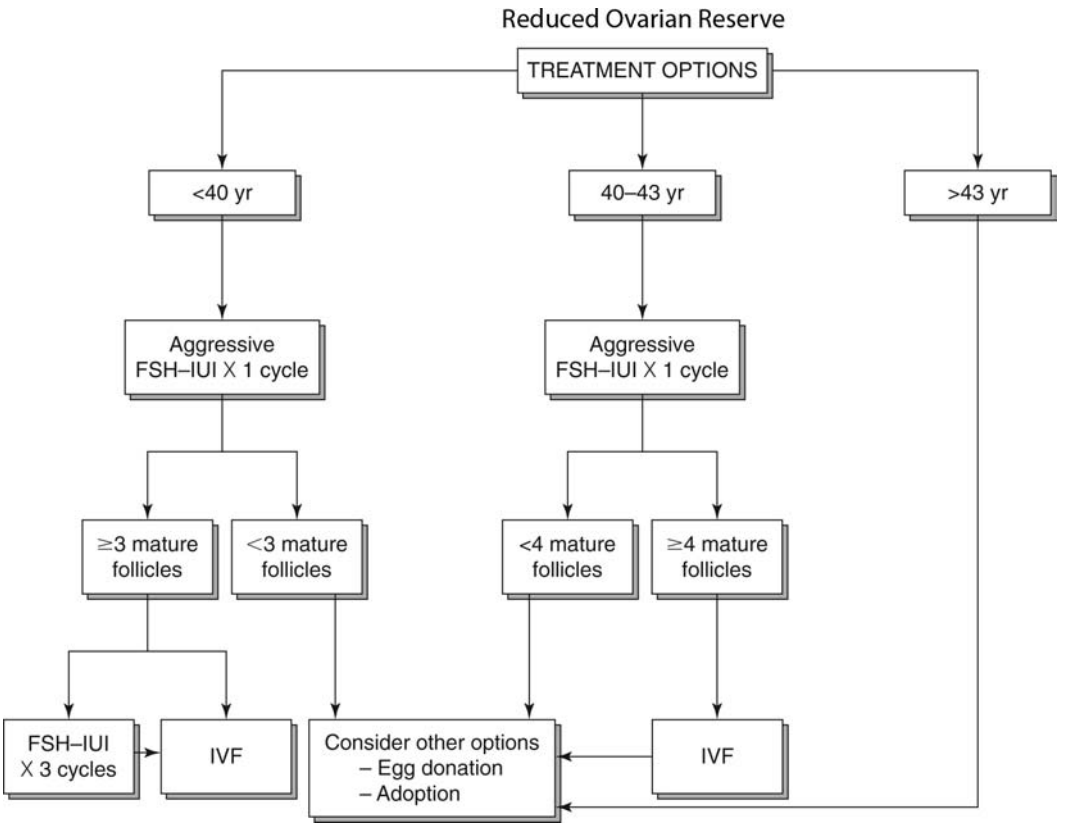

Figure 5.3 Reduced ovarian reserve. *Abbreviations*: FSH, follicle-stimulating hormone; IUI, intrauterine inseminations; IVF, in vitro fertilization.

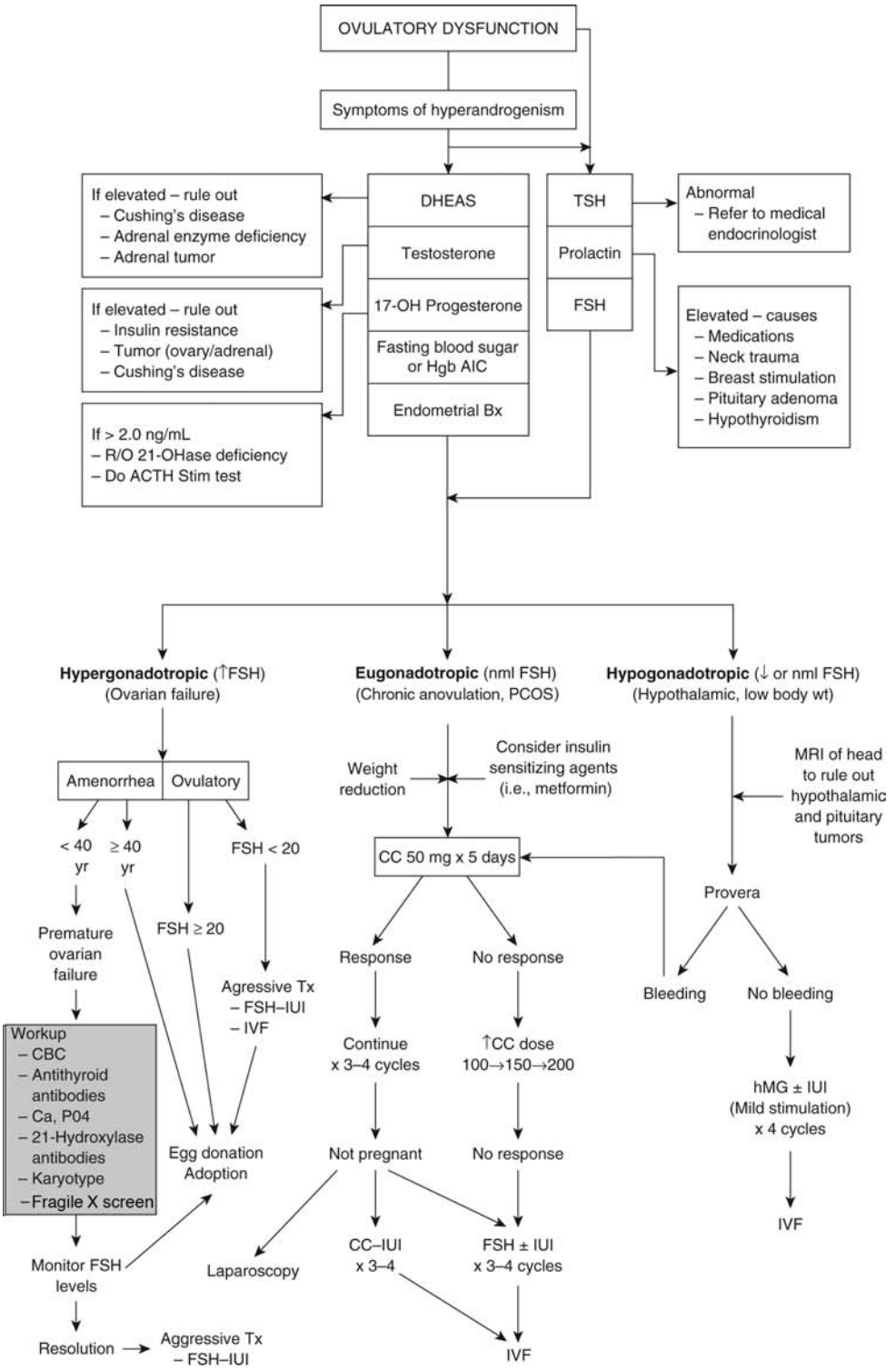

Figure 5.4 Ovulatory dysfunction. *Abbreviations*: DHEAS, dehydroepiandrostenedione; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging; PCOS, polycystic ovarian syndrome; CC, clomiphene citrate; IUI, intrauterine inseminations; IVF, in vitro fertilization; CBC, complete blood count; hMG, human menopausal gonadotropins.

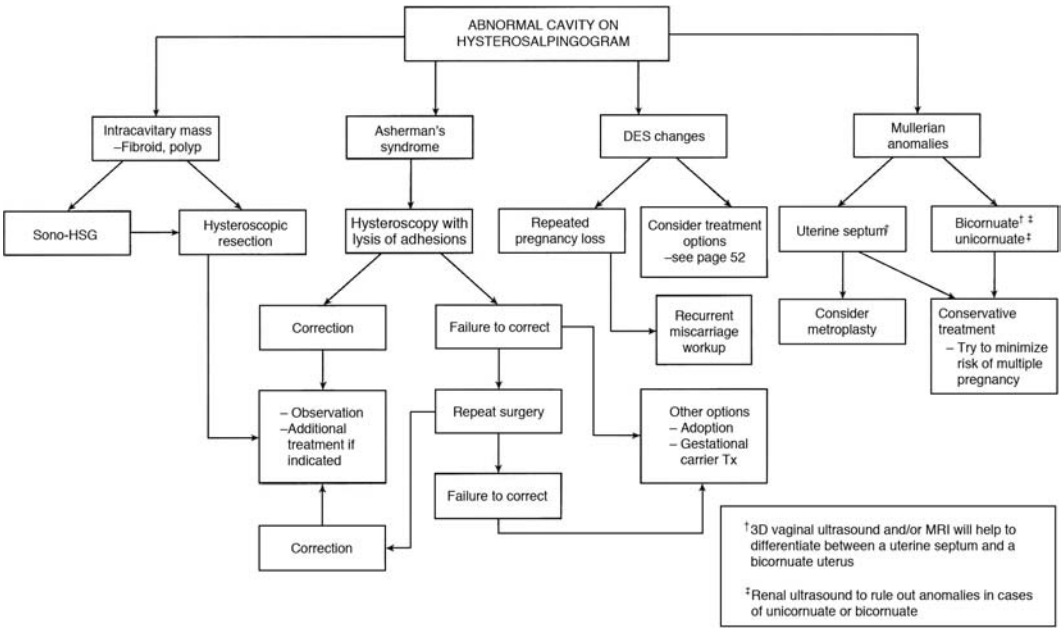

Figure 5.5 Uterine factor. *Abbreviations*: Sono-HSG, sonohysterogram; DES, diethylstilbestrol; MRI, magnetic resonance imaging.

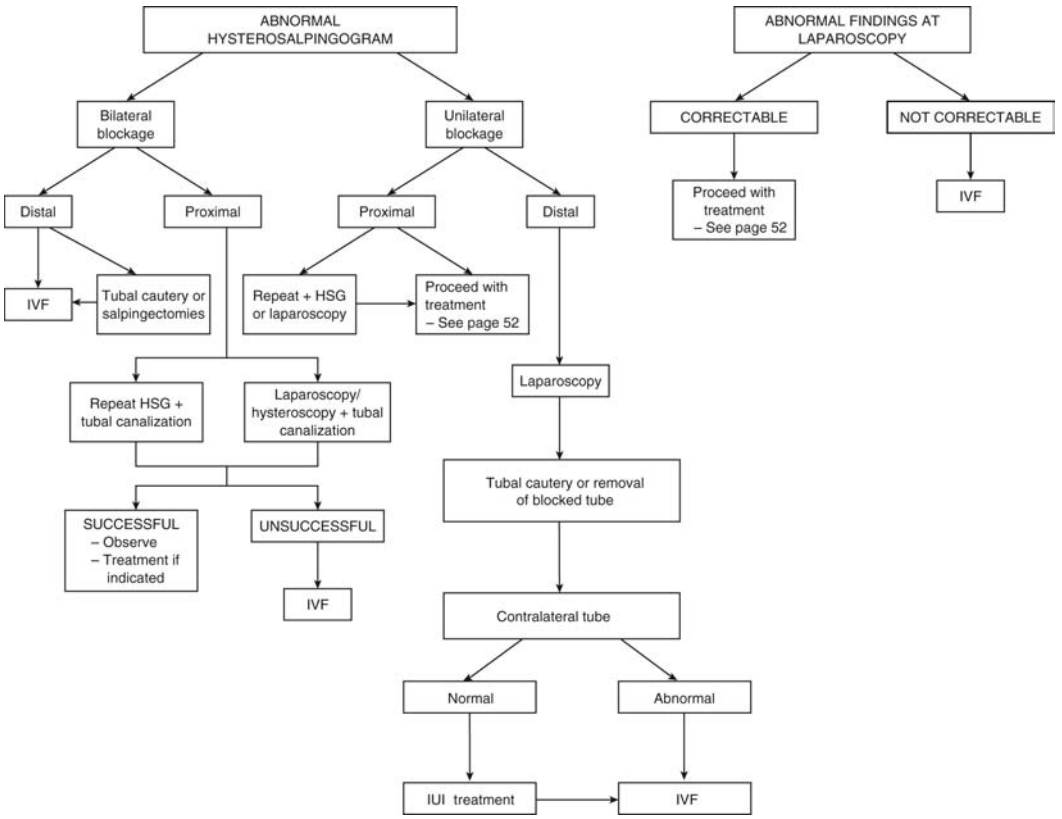

Figure 5.6 Tubal/peritoneal factor. *Abbreviations*: IVF, in vitro fertilization; HSG, hysterosalpingogram; IUI, intrauterine inseminations.

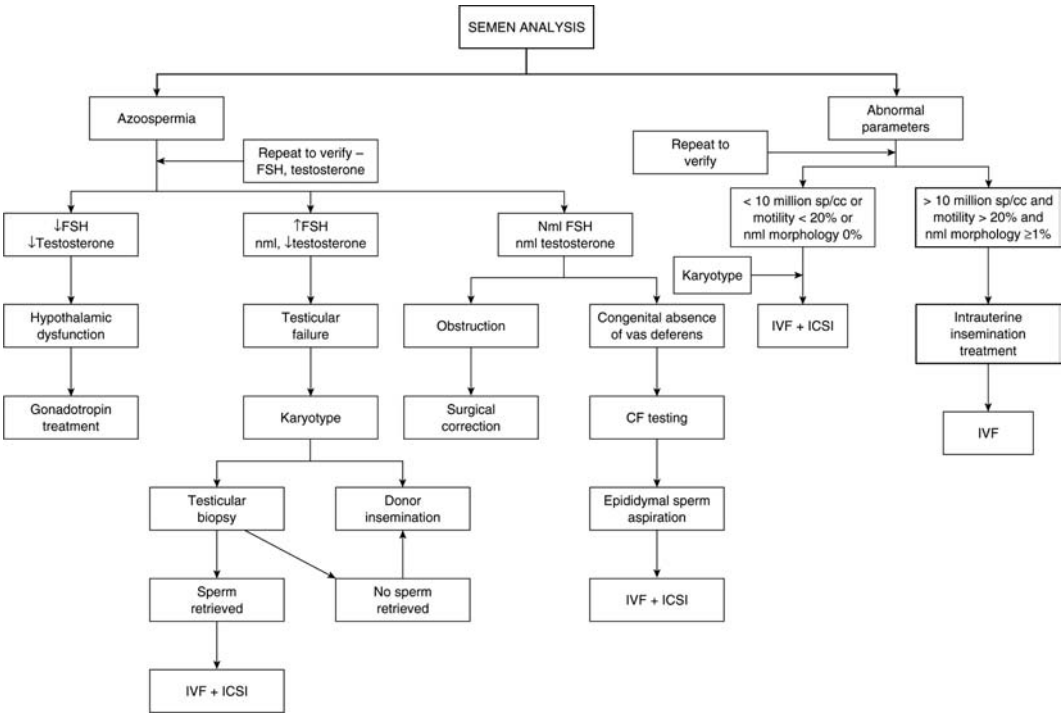

Figure 5.7 Male factor. *Abbreviations*: FSH, follicle-stimulating hormone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; CF, cystic fibrosis.

6 Treatment options I. Ovulation induction

Selwyn P Oskowitz

Approximately 20% of infertile patients present with underlying ovulatory dysfunction as a major contributing factor to their infertility. Compared to other etiologies, ovulatory problems are often the easiest to correct in most cases. However, before any treatment is started, it is important to delineate the underlying cause of the ovulatory dysfunction (refer to clinical algorithms in chap. 5). The causes of ovulatory dysfunction are varied and can be categorized into *hypergonadotropic* (ovarian failure), *eugonadotropic* (chronic anovulation), and *hypogonadotropic* (hypothalamic, weight-related) states. Women who have ovarian failure or are perimenopausal generally do not respond favorably to medical treatment. There are many different medications, both oral and injectable, which can be used as part of ovarian stimulation. The choice of medication depends on the clinical presentation and the goal of the specified treatment. This chapter reviews the current approach to ovulation induction.

Box 1 Definition of terms

Ovulation induction is the term for the stimulation of ovulation in the anovulatory patient. The aim is to stimulate the growth of a single follicle with the release of its egg.

Superovulation (SO) is the term for stimulating the growth of multiple follicles with the release of multiple eggs. SO is an integral part of intrauterine insemination and in vitro fertilization (IVF) treatments.

CLOMIPHENE CITRATE

Clomiphene citrate (CC) was first introduced over 50 years ago and is the most commonly prescribed medication for the infertile woman. It can be prescribed for different reasons, but its primary indication is for the correction of ovulatory dysfunction. When compared to other ovulation induction agents, CC is inexpensive, easy to administer, and does not require close monitoring that is required with injectable ovulation induction agents. CC is the first-line treatment for those patients with polycystic ovary syndrome (PCOS). Those patients with hypothalamic dysfunction who fail to have withdrawal bleeding following a progesterone challenge will, in most cases, not respond well to CC. Failure to bleed from progesterone indicates a low estrogenic state, and CC needs to compete with estrogen to exert its effect on the hypothalamus and pituitary.

Pharmacology

CC is a triphenylethylene derivative that is related to tamoxifen and diethylstilbestrol (DES). CC exists in two isomeric forms, zuclomiphene and enclomiphene citrate. The pharmacological effect of this medication is from the zuclomiphene citrate isomer. The two available agents, Serophene® and Clomid®, contain equal amounts of these two isomers. CC is an estrogen antagonist and binds for an extended period of time to intranuclear estrogen receptors, which decreases the replenishment of these receptors. The hypothalamus responds to the "pseudo-hypoestrogenic" state by increasing gonadotropin-releasing hormone (GnRH) pulse frequency, which, in turn, increases the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. CC has a half-life of five days and can be detected in the blood up to six to eight weeks after administration. Despite the long half-life of CC, there is no reported increase in congenital anomalies that can be attributed to the use of this medication.

Side Effects

Since CC is a synthetic hormonal agent, side effects are common and are not dose related. Many of the side effects that result are related to the *pseudo*-hypoestrogenic state that is created. The more common side effects and their incidence are as follows:

20%: irritability, mood changes
10%: vasomotor symptoms
6%: abdominal discomfort
2%: breast discomfort
2%: nausea/vomiting
1%: visual symptoms
1%: headaches

The use of ovulation induction agents, especially CC, may result in more pain associated with ovulation. Prolonged administration of CC through its antiestrogenic action can diminish cervical mucus production and thin the endometrial lining, which could lower the chance of pregnancy.

Dosage and Administration

CC is available in 50 mg tablets. The initial recommended dose of CC is 50 mg daily for five days starting on cycle days 2, 3, 4, or 5 following either a spontaneous or progesterone-induced menstrual period. After the treatment is started, if the menstrual cycle is <32 days in length, then the current dose should be continued for three cycles. Couples should be instructed to use an ovulation predictor kit or to time intercourse around the predicted periovulatory period. If the induced cycles are >32 days, the dosage of the CC should be increased to 100 mg for five days. If this dose is inadequate, then the dose should be increased to 150 mg. If pregnancy is not achieved after three ovulatory cycles, then other factors should be ruled out. If no other factors are identified, then intrauterine inseminations can be added to the CC treatment since CC may have an adverse affect on cervical mucus in 15% of cases. Although higher doses up to 250 mg/day may be attempted, the majority of pregnancies occur at dosages of 150 mg daily or less. If the patient with chronic anovulation does not respond to a dose of 150 mg daily, then our approach is to proceed on with injectable gonadotropins.

Outcome

Proceeding in the stepwise fashion as described above, the ovulatory rates on the 50-, 100-, and 150-mg dosage regimens are 50%, 22%, and 12%, respectively (1). However, despite 80% of patients ovulating with CC treatment, only 40% to 50% will achieve pregnancy (2).

Pregnancy rate: 10% per ovulatory cycle
Multiple pregnancy rate: 8% to 10% (most are twins but there is a 1% chance of triplets)

Box 2 Management of CC failures

Lack of ovulation:

- Increase CC dose up to 250 mg/day. In clinical experience, doses beyond 150 mg/day are rarely effective
- Serial increases in CC dose without a new period, if no sign of follicle growth 14 days after the last CC dose (3)
- Metformin pretreatment with 1500 to 2000 mg qd for four to six weeks prior to another course of CC (4)
- Dexamethasone 0.5 mg po qd for cases where the dehydroepiandrostenedione (DHEAS) is over 200 mg/dL

Ovulation but no pregnancy:

- Add a surrogate LH surge with an injection of human chorionic gonadotropin (hCG) 10,000 units or Ovidrel® 250 μg subcutaneously when the lead follicle is 18 to 25 mm in diameter

- Improving cervical mucus with
  - Estradiol 2 mg daily from cycle day 9 to ovulation
  - Robitussin® (plain) one teaspoon three times daily or guafenesin tablets 600 mg bid beginning cycle day 9 through ovulation
- Combined approach of estradiol from day 12 followed by progesterone starting three days after the LH surge detected by ovulation predictor kit (5)
- Add intrauterine inseminations

Unexplained Infertility

In clinical practice, CC is commonly prescribed for the woman with unexplained infertility. Theoretically, it seems that CC would improve fecundity by increasing the number of eggs that are released at the time of ovulation and may correct subtle ovulatory dysfunction. However, previous studies including a recently published Cochrane review of seven trials fail to show that CC improves fertility over doing nothing at all (6–8). Nevertheless, some couples and clinicians feel that this is a reasonable initial treatment to pursue. As with any therapy, most pregnancies are achieved within the first few months of treatment. Therefore, the duration of treatment should be limited to three to four cycles at which time the treatment plan should be reassessed.

Recommended dosage: CC 100 mg administered between cycle days 3 and 7. Limit duration of treatment to three to four months. Instruct couples to use an ovulation predictor kit or have intercourse every other day between cycle days 10 and 18.

Pregnancy rate: 6% per cycle

LETROZOLE

Letrozole (Femara®) is an aromatase inhibitor that is a supplemental treatment for hormonally responsive breast cancer. There has been interest in the utility of this medication as a fertility drug, but it is not FDA approved for this indication. The use of letrozole in the infertile population was the topic of a recent review (9). By inhibiting the aromatase enzyme, letrozole causes a drop in estrogen levels, which results in release of FSH by the pituitary gland. Unlike CC, letrozole does not have detrimental effects on the cervical mucus and endometrial lining. Letrozole is available in 2.5 mg tablets and is taken once a day beginning in the early follicular phase. The standard dose is 2.5 mg/day increasing up to 7.5 mg a day for five days. The incidence of side effects with letrozole is similar to that noticed with CC, including hot flashes, nausea, dizziness, and headaches. The risk of a multiple pregnancy is from 5% to 10%, most of which are twins, and high-order multiple pregnancies are rare. Ovarian hyperstimulation syndrome (OHSS) is theoretically possible.

Note: There was an initial report concluding that there was an increased rate of fetal anomalies with letrozole (10). However, larger studies have ***not*** *shown any increased risk to the offspring (11,12). Despite this reassurance, patients should be counseled that this medication is* ***not*** *FDA approved for ovulation induction purposes.*

OTHER MEDICATIONS THAT CAN BE USED WITH CC

In some women with ovulatory dysfunction, other medications that can be administered by themselves or in addition to CC may be considered.

Oral Hypoglycemic Agents

It is now believed that insulin resistance plays a central role in the pathogenesis of PCOS. Insulin resistance is a condition in which the action of insulin is hampered by either a defective insulin receptor or a postreceptor defect. With insulin resistance, higher circulating levels of insulin are necessary to maintain normal glucose homeostasis. Hyperinsulinism can explain many of the associated findings of PCOS. Insulin increases ovarian and adrenal androgen production, decreases the production of sex hormone binding globulin, and stimulates the pituitary secretion of LH. All this leads to an androgenic milieu that interferes with the normal

follicular development and ovulation. Insulin resistance is a metabolic disorder and ovulatory dysfunction is only one of its manifestations. Other medical issues associated with insulin resistance include type II diabetes, hypertension, dyslipidemia, centripetal obesity, and an increased risk of cardiovascular disease.

Patients with adult-onset diabetes mellitus have been treated effectively with oral hypoglycemic agents, such as metformin, which improves the actions of insulin in several ways. It increases the uptake of glucose into fat and muscle cells. In addition, it decreases intestinal absorption of glucose and reduces hepatic gluconeogenesis. There is published data that has confirmed that metformin improves the insulin resistance in patients with PCOS, which results in correction of the ovulatory dysfunction (4,13,14). This was a significant breakthrough in the treatment of PCOS. Many women with PCOS respond poorly to CC and have to be treated with injectable gonadotropins to induce ovulation which is associated with a higher multiple pregnancy rate and greater chance of OHSS. In a previous meta-analysis, it was concluded that metformin alone improved the rate of ovulation (15,16). The ovulation rates were different between the metformin and placebo groups, 46% versus 26%. Also the rate of ovulation in those who took metformin plus CC or CC alone was 76% versus 42%, respectively. While metformin may be effective by itself, it may take up to six months to appreciate ovulatory cycles (14,16). After these studies were published, it was felt by many infertility specialists that metformin treatment should be the initial treatment for PCOS patients. However, many of the initial studies included a small number of patients. A well-designed study published by Legros et al. provided the data that helped to define the role of metformin treatment in PCOS (17). This multicenter blinded study involved 626 infertile women with PCOS who were randomly assigned to one of three arms: clomiphene citrate plus placebo (CC), metformin plus placebo (MET), and metformin plus clomiphene citrate (MET/CC). Patients were then followed for six months after the treatment was begun. The live birth rate was 22.5% in the CC group, 7.2% in the MET group, and 26.8% in the MET/CC group. The difference in pregnancy rates was statistically significant between CC versus MET and MET/CC versus MET groups but not for CC versus MET/CC. The conclusion of this study is that initial treatment with CC for the PCOS patient is warranted. However, metformin does have a role in the treatment of the PCOS patient, which is discussed below.

Evaluation

Renal studies [creatinine, blood urea nitrogen (BUN)] and liver function tests [serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT)] should also be obtained. One potential risk of metformin treatment is lactic acidosis. The incidence of this side effect is increased in patients with renal or hepatic dysfunction.

Recommended Dosage

Metformin is available in 500-mg or 750-mg extended-release (XR) tablets. Initiation of metformin should be done in a gradual fashion to decrease the incidence of side effects. One tablet (500 mg) should be taken daily for one week, then one tablet twice a day for one week, and then one tablet three to four times a day (1500–2000 mg/day). The medication should be taken with meals.

Side Effects

Gastrointestinal symptoms, including nausea, vomiting, diarrhea, bloating, and flatulence, occur in 30% of patients who take metformin. These side effects are usually temporary, but in some patients the side effects do not abate. In such cases, reducing the dose may reduce the side effects, and then at some time in the future the dose can be increased. Lactic acidosis is a serious metabolic disorder that may be increased in patients with renal and/or hepatic dysfunction. There have been reports of metformin-induced lactic acidosis following the administration of intravenous iodine contrast agents, which can result in transient nephrotoxicity. Therefore, metformin should be withheld 24 hours before to 48 hours after the performance of the X-ray procedure. Metformin is a schedule B drug but should be

discontinued when pregnancy is established. PCOS patients are at increased risk of miscarriage, and there has been some controversy as to whether metformin decreases the chance of a first-trimester loss if taken throughout the early part of pregnancy. In a recent meta-analysis, it was concluded that metformin does *not* decrease the chance of a first-trimester loss (18).

Clinical Application

Long-term treatment. In some cases, long-term treatment with metformin can be considered for up to 6 to 12 months. This is an especially attractive treatment for those women with obesity and possibly other associated consequences of insulin resistance (i.e., hypertension, glucose intolerance) who may not be in the best health for a pregnancy. It would also be considered in those women who want to avoid a multiple pregnancy that is associated with ovarian stimulation medications. For the patient with obesity, good nutrition and an exercise program should be stressed. A referral to a nutritionist should strongly be considered. Weight loss will increase the effectiveness of metformin. The patient should follow-up with the physician periodically every six to eight weeks to monitor for treatment efficacy.

Short-term treatment. For those patients who have failed to respond to moderate doses of CC, pretreatment with metformin (four to eight weeks) before moving on to another cycle of CC may prove efficacious.

Dopaminergic Agents

Hyperprolactinemia is a cause of ovulatory dysfunction. A serum prolactin assay should be obtained on any woman who presents with irregular or absent menstrual periods and/or galactorrhea. It is important that the prolactin level is assessed on a blood sample drawn in the morning (around 10 o'clock) during the follicular phase of the menstrual cycle. At other times of the day, and in the luteal phase, physiological elevations of prolactin can occur. If an elevated prolactin level is found, the assessment should be repeated for verification. If a woman is found to have persistent hyperprolactinemia, then a cause should be determined. Hyperprolactinemia can be secondary to previous breast surgery, neck trauma, medication use, renal insufficiency, a pituitary tumor, and hypothyroidism. Any woman with unexplained hyperprolactinemia when associated with ovulatory dysfunction should have a MRI of the brain to rule out a pituitary tumor. Several dopaminergic agents are available to correct the hyperprolactinemia (e.g., bromocriptine, cabergoline). Many times, these agents are effective by themselves in correcting the ovulatory dysfunction. In a previous review reporting on 22 clinical trials, it was noted that 80% of women with hyperprolactinemia had restoration of their menstrual function (19). On average, menstrual function returned 5.7 weeks after treatment was started. If the patient fails to develop normal ovulatory cycles despite the establishment of a normal prolactin level, then the clinician may consider adding CC or another ovulation induction agent to the treatment regimen.

How do we explain the woman who has normal menstrual cycles in the presence of hyperprolactinemia? In addition to the biologically active monomeric prolactin, other larger prolactin species (termed "macroprolactins") are present. These macroprolactins are inactive but are measured in the conventional prolactin assay. A macroprolactin level can be measured to determine the true circulating levels of bioactive prolactin. For this reason, routine screening of women with normal cycles and no complaints of galactorrhea should be discouraged.

Available Agents and Doses

1. *Bromocriptine (Parlodel®)*: It is available in 2.5 mg tablets. Start with half a tablet (1.25 mg) qhs for one week and then increase up to one tablet (2.5 mg) qhs. Repeat prolactin level in two to three weeks. If the prolactin level is still elevated, the dose can be increased in an incremental fashion.
2. *Cabergoline (Dostinex®)*: It is available in 0.5 mg tablets. Start with one tablet (0.5 mg) twice a week. Dose may be increased by 0.25 mg twice weekly to $\leq$1 mg twice a

week, depending on the serum prolactin level. Do not increase the dose more often than every four weeks.

Side Effects
The more common side effects include gastrointestinal upset, fatigue, dizziness, and nasal stuffiness. For those with persistent gastrointestinal side effects, vaginal administration of the medication may be considered.

Dexamethasone

Dexamethasone can be considered for the anovulatory woman who fails to respond to increasing doses of CC or is noted to have an elevated DHEAS level. An elevated DHEAS level may suggest an attenuated adrenal enzyme deficiency. Other causes include an adrenal tumor and Cushing's syndrome, which must be considered but are, nonetheless, rare. If associated with an elevated 17-OH progesterone level, a 21-hydroxylase deficiency must be ruled out. The administration of dexamethasone will decrease the adrenal androgen contribution to the pool of androgens. In some cases, this will be enough to improve the response to CC. Dexamethasone can be administered at night at a dose of 0.5 mg. One month after starting the dexamethasone, a morning cortisol level should be checked. A cortisol level <2 μg/dL suggests significant depression of cortisol synthesis by the adrenal gland, which could interfere with a stress response by the adrenal gland. Under this circumstance, the dose or frequency of administration should be decreased. The use of dexamethasone should be avoided during pregnancy.

Dexamethasone can be considered in other clomiphene failures in the absence of elevated androgen levels. In a previous prospective study, 223 CC-resistant patients were randomized to receive CC 200 mg days 5 to 9 plus dexamethasone (DEX) 2.0 mg days 5 to 14 and the other group was given CC 200 mg days 5 to 9 plus a placebo (20). In the CC-DEX group, 88% ovulated compared to only 20% in the CC-placebo group.

Dexamethasone treatment options:

- 0.5 mg qd. Check morning serum cortisol plasma level three to four weeks after treatment started, and if <2.0 μg/dL, reduce the dose
- 2.0 mg cycle days 5 to 14 during CC cycle

Gonadotropins

Gonadotropins are injectable medications that are effective in correcting ovulatory dysfunction. A list of current agents that are available appear in chapter 8. The agent used depends on the clinical presentation. One must exercise caution when administering these agents to correct ovulatory dysfunction (as compared to their use in the context of superovulation) to minimize the risk of multiple pregnancy.

Hypothalamic Dysfunction
Since these patients are deficient in FSH and LH, both these hormones need to be replaced. Therefore, either human menopausal gonadotropins (hMG; Menopur®, Repronex®) alone or FSH injections supplemented with LH (Luveris®) can be administered. It is important that low doses (75 IU) be administered initially and one is cautious in raising the dose.

1. Administer hMG 75 IU ×; 5 to 7 days, and then check E2 and US.
   a. If E2 <50 increase by 37.5 IU ×; 3 days, then repeat the E2/US. Increase hMG by no more than ½ amp every three to four days.
   b. If E2 >50, continue the same dose and repeat monitoring two to three days.
2. Administer hCG when lead follicle is ≥ 16 mm.

Caution: These patients are at significant risk of a multiple pregnancy—the goal of the stimulation is one to two follicles. If more than two follicles ≥16 mm or if several secondary follicles >12 mm are present, then consideration should be given to canceling the cycle.

OHSS can be a severe risk related to gonadotropin use. In addition to the aforementioned mature follicles, careful study of the ultrasounds is needed to assess the number of small follicles (10–14 mm).

Polycystic Ovarian Syndrome

These patients are deficient in FSH and may have elevated circulating levels of LH. Therefore, only FSH-containing medications (Gonal F®, Bravelle®, Follistim®) are needed to correct the ovulatory dysfunction.

1. Administer FSH 75 IU ×; 5 days, and then check E2 and US.
   a. If E2 <50 increase by 37.5 IU ×; 3 days, then repeat the E2/US. Increase hMG by no more than ½ amp every three to four days.
   b. If E2 >50, continue the same dose and repeat monitoring two to three days.
2. Administer hCG when lead follicle is ≥16 mm.

Caution: These patients are at risk of a multiple pregnancy and OHSS—the goal of the stimulation is one to two follicles. However, the success rate in the PCOS population is lower than that in patients with hypothalamic dysfunction. If more than three to four follicles ≥16 mm develop on ultrasound examination or if several secondary follicle >12 mm are present, then consideration should be given to canceling the cycle.

REFERENCES

1. Gysler M, March CM, Mishell DR, et al. A decade's experience with an individualized clomiphene treatment regimen including its effect on the post-coital test. Fertil Steril 1982; 37:161.
2. Practice Committee of the American Society for Reproductive Medicine. The use of clomiphene citrate. Fertil Steril 2006; 86:S187–S193.
3. Hurst B, Hickman M, Matthews R, et al. A novel clomiphene 'stair-step' protocol reduces time to ovulation in women with polycystic ovary syndrome. Am J Obstet Gynecol 2009; 200:510.
4. Nestler JE, Jakubowicz DJ, Evans WS, et al. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998; 338:1876–1880.
5. Elkind-Hirsch KE, Phillips K, Bello SM, et al. Sequential hormonal supplementation with vaginal estradiol and progesterone gel corrects the effect of clomiphene on the endometrium of oligo-ovulatory women. Hum Reprod 2002; 17:295–298.
6. Hughes E, Brown J, Collins JJ, et al. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev 2010; 20(1):CD000057.
7. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod 1997; 12:1865–1872.
8. Fujii S, Fukui A, Fukushi Y, et al. The effects of clomiphene citrate on normally ovulatory women. Fertil Steril 1997; 68:997–999.
9. Requena A, Herrero J, Landeras J, et al. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Hum Reprod Update 2008; 14:571–582.
10. Biljan MM, Hemmings R, Brassard N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. Fertil Steril 2005; 84(suppl 1):S95.
11. Tulandi T, Martin J, Al-Fadhli R, et al. Congenital malformations among 9111 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril 2006; 85(6):1761–1765.
12. Forman S, Gill R, Moretti M, et al. Fetal safety of letrozole and clomiphene citrate for ovulation induction. J Obstet Gynaecol Can 2007; 29:668–671.
13. Velazquez EM, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997; 90:392–395.
14. Velazquez EM, Mendoza SG, Hamer T, et al. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994; 43:647–654.
15. Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 2003; 327:951–957.
16. Ibanez L, Valls C, Ferrer A, et al. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab 2001; 863:595–598.

17. Legros RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in polycystic ovary syndrome. N Engl J Med 2007; 356:551–566.
18. Paolmba S, Falbo A, Orio F, et al. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2009; 92:1646–1658.
19. Cuellar FG. Bromocriptine mesylate (Parlodel) in the management of amenorrhea/galactorrhea associate with hyperprolactinemia. Obstet Gynecol 1980; 55:278.
20. Parsanezhad ME, Alborzi S, Motazedian S, et al. Use of dexamethasone and clomiphene citrate in the treatment of clomiphene-resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospective, double-blind, place-controlled trial. Fertil Steril 2002; 78:1001–1004.

7 Treatment options II. Intrauterine inseminations

Steven R Bayer

Intrauterine insemination (IUI) was introduced over 50 years ago and is one of the most commonly administered fertility treatments. It is a rational treatment for infertility secondary to a cervical factor, mild male factor, and ejaculatory dysfunction, but the most common indication is unexplained infertility. It is also the best approach to therapeutic donor sperm insemination (TDI). In cases of TDI, a nonmedicated or natural cycle is used initially, but for other indications this approach has a low success rate. Therefore, the use of fertility medications to increase the development of multiple follicles is an important part of IUI treatment and has been shown to increase the chance of success. In addition, the success rate with ovulation induction plus IUI is higher than that with ovulation induction alone. How does an IUI increase the chance of pregnancy? The explanation remains obscure, but it may be the result of several factors. The sperm washing procedure may eliminate toxins or bacteria in the seminal plasma and has been shown to induce the acrosome reaction causing activation of the sperm. Performance of the IUI may bypass an impediment in the cervical mucus. In contrast to intercourse, the IUI results in a higher number of motile sperm that find their way into the uterine cavity. Finally, the IUI may overcome faulty coital technique on the part of the couple. Despite all of these theoretical benefits of IUI, the overall success of IUI treatment is low in comparison to in vitro fertilization (IVF). Nevertheless, for many infertility patients, IUI is their first introduction to treatment. This chapter provides an overview of the treatment.

APPROACHES TO IUI TREATMENT

Natural Cycle

A natural or nonmedicated approach is most often used with TDI, but in the context of infertility, this approach is associated with a low success rate. However, it might be the desire for the couple who wants to completely avoid medications or a multiple pregnancy. This is not considered an option for a woman with ovulatory dysfunction.

Monitoring

The patient is instructed to start testing her urine with an ovulation predictor kit three to four days before the anticipated time of ovulation. The woman who has cycles that are 28 to 30 days in length is instructed to start testing her urine on day 11. When the ovulation predictor test turns positive, she is instructed to come in the following day for the insemination.

Clomiphene Citrate

Clomiphene citrate (CC) can be the initial medicated approach for younger women under the age of 35. For women over the age of 35, a more aggressive ovulation induction (e.g., gonadotropins) is the preferred approach. CC is the most widely prescribed fertility medication. For a detailed description of this medication, refer to chapter 6. CC is administered at a dose of 100 mg for five days between cycle days 3 and 7.

Monitoring

The patient is instructed to use an ovulation predictor kit beginning on cycle day 11. When the test turns positive, a single insemination treatment is done the following day. In our experience, approximately 90% of patients will detect the luteinizing hormone (LH) surge between cycle days 11 and 15. An alternative is to perform vaginal ultrasound examinations beginning cycle day 12 and to administer human chorionic gonadotropin (hCG) (10,000 IU, or 250 μg of Ovidrel®) when the follicle reaches 18 mm and the insemination is scheduled

Table 7.1 Boston IVF CC-IUI Success Rates

Age (yr)	Pregnancies achieved		Pregnancies achieved after 3 cycles of treatment (%)
	Per cycle (%)	Per patient (%)	
<35	11.5	24.2	89.5
35–37	9.2	18.5	91
38–40	7.3	15.1	95
41–42	4.3	7.4	67
>42	1.0	1.8	100

A pregnancy was defined as ultrasound confirmation of an intrauterine sac.
Source: From Ref. 2.

36 hours later. There is no difference in the success rate with CC-IUI when ultrasound monitoring and hCG trigger are used versus monitoring the LH surge with urine testing (1). However, the advantage of doing ultrasound examinations is that they provide valuable information about the ovarian response. If just a single follicle develops, then there should be consideration to substituting follicle-stimulating hormone (FSH) injections for the CC. The average success rate following CC-IUI treatment is 8% to 10% per cycle and the multiple pregnancy rate is 10% (9%, twins; 1%, triplets). An important factor that impacts on treatment success is the maternal age. The Boston IVF experience with CC-IUI of more than 4000 cycles was reported by Dovey et al. (2) and the results are reported in Table 7.1.

Gonadotropins

The use of FSH injections for ovulation induction as part of IUI treatment increases the success rate. For a detailed discussion on these medications, the reader is referred to chapter 8. The injections of FSH are started on day 3 and continued until mature follicles have developed. The initial dose will be dependent on many factors including previous response and age. In general, the first cycle of treatment requires more caution with the starting dose (75–150 U), since it is unknown how the patient will respond to the medication. This is of less concern for the older patient over the age of 40 who most likely has some reduced ovarian reserve and the starting dose may be increased to (150–225 U). The goal of the treatment may vary as well. For a younger woman, the goal is to obtain two to four mature follicles that are 16 mm or larger. If more than five mature follicles are present and/or there are multiple follicles between 12 and 16 mm, then there is an increased risk of a multiple pregnancy. These cycles should be either canceled or converted to an IVF treatment cycle. For the woman over the age of 40, the chance of a multiple pregnancy is reduced and the goal of the stimulation is to obtain four to six mature follicles.

Monitoring

A serum estradiol level and vaginal ultrasound examination is recommended four to five days after starting injections. If the estradiol level is >400 pg/mL, then the dose is reduced by 75 U. The goal is to have the estradiol level increased by 50% to 100% every two to three days. The vaginal ultrasound will determine the number and size of the follicles. A mature follicle is between 16 and 20 mm in diameter. The final goal of the treatment is to have a peak estradiol level between 500 and 2000 pg/mL at the time of the hCG administration. A single insemination is performed 36 hours after hCG administration.

SUCCESS RATE

As with any fertility treatment, several factors impact success. One important factor is the semen quality. Pregnancy rates are higher when the total motile sperm count is >2 million, postwash motility is >40%, and/or normal sperm morphology is >4% (3). However, interpretation of sperm morphology can vary from laboratory to laboratory. Age is an important determinant of treatment success (4,5). Duran et al. reported on over 1000 cycles and the live birth rate in the different age groups to be as given in Table 7.2.

Table 7.2 FSH IUI Success Rates

Age (yr)	Number of cycles	Live birth rate, % (95% CI)
<25	15	26.7 (4.3–49.4)
25–29	219	14.2 (9.6–18.8)
30–35	556	12.5 (9.8–15.2)
36–39	221	9.5 (5.6–13.4)
≥40	106	8.5 (3.2–13.8)

Source: From Ref. 5.

In comparison to CC-IUI, success rates following FSH-IUI tend to be higher, but one must also take into consideration the increased multiple pregnancy rate of 15% to 20%, which includes a higher incidence of high-order multiple pregnancies.

PREPARATION OF THE SEMEN SAMPLE

A semen sample is produced on the day of the IUI. It is preferable that the semen sample is produced on site, but it can be produced at home and then transported to the laboratory as long as it can be delivered within 60 minutes after production. The sample should be kept at body temperature. The sperm concentration and motility of the semen sample are assessed. The semen sample is then washed and prepared. Washing of the sample removes prostaglandins and bacteria and it also concentrates the sperm by removing the seminal plasma. For security reasons, we only accept sperm samples from the husband and not another party (including the wife). His identification is confirmed by examination of his driver's license. Our sperm washing procedure is as follows:

Process all specimens using sterile technique and practicing universal precautions. Latex gloves should be worn at all times, and facial protection should be used if the sample is not processed under a hood. Check comments section of the schedule for any special instructions.

1. The semen sample is produced by masturbation into a labeled noncoated, sterile container after two to three days of abstinence. Lubricants should not be used to produce the sample.
2. Allow semen sample to liquefy for 20 to 60 minutes.
3. Measure the volume with a 10-mL pipet.
4. Divide the sample into two test tubes labeled "pellet" with patient's name.
5. Add an equal volume of sperm wash to each of the tubes and mix well.
6. Remove any coagulates that may pellet to bottom of tubes.
7. If viscosity still exists, chymotrypsin may be used.
8. Centrifuge for 10 minutes at 1200 rpm (300 x *g*).
9. Remove the supernatant and place in labeled "super" tube.
10. Resuspend the pellets in a total of 2 mL fresh sperm wash; the two pellet tubes should be combined at this step. The wash medium should not exceed 2 mL.
11. Centrifuge (second time) for 5 minutes at 1200 rpm (300 x *g*).
12. Remove the supernatant.
13. Resuspend the pellet in a total of 0.5 mL sperm wash.
14. Mix thoroughly and count the sample.
15. Place washed sample on the 37°C warmer until ready to use.

Performing the IUI

Our nurses are trained to perform the IUIs. If there is any difficulty with the insemination, then a physician is called to complete the procedure. Before the insemination, the patient's name is verified and she confirms that her name is on the tube containing the washed sperm sample. To perform the IUI treatments, a speculum examination is performed and the cervix is visualized. The cervix is wiped with a large cotton tip applicator. The washed sperm sample is loaded into a catheter, which is inserted through the cervical canal and into the uterine cavity.

Immediately following the IUI, the patient is discharged and normal activity can be resumed. A pregnancy test is scheduled 14 days later.

Single Vs. Double Inseminations

The decision to do one versus two inseminations has been the subject of ongoing debate. In a recent meta-analysis, Polyzos et al. reported on 6 randomized controlled studies including 829 women (6). The pregnancy rate in double versus single insemination groups was 13.6% versus 14.4%, respectively; the difference was not statistically significant. Osuna et al. reported on eight randomized controlled studies (7). The pregnancy rate for double vs single insemination groups was 13.30% vs. 10.2%, respectively. The odds ratio was 1.33 (95% CI 0.99, 1.73) in support of a double insemination. However, two of the studies included used CC as a stimulatory agent. Both of these studies using CC confirmed a benefit of a second insemination. The explanation as to why a second insemination is needed with CC remains uncertain. When the CC studies were excluded the results did not confirm that the additional IUI improved the success. In a recent study published by Bagis et al. there was no difference in pregnancy rates whether one or two inseminations were performed (8). The data published to date does not support the need for a second insemination.

COST ANALYSIS

Another factor that must be considered in the decision making process is cost. Massachusetts has an insurance mandate that provides complete coverage for the costs of treatment. The disadvantage is that a certain number of IUI treatments must be completed before approval is given to move on to IVF treatment. Most patients throughout the country do not have insurance coverage and are therefore self-pay. The approximate cost of CC-IUI, FSH-IUI, and IVF including medications is $500, $2500, $7000 to $10,000, respectively. When one considers the overall success rates following the various treatments, for some patients it makes sense to try CC-IUI; and if this proves unsuccessful, then move on to IVF.

COMMENTARY

As IVF success rates have continued to increase, the indications to do IUI will diminish. CC-IUI treatment is a cost-effective treatment and will continue to be a treatment option. However, FSH-IUI treatment is more costly, associated with a higher chance of a high-order pregnancy, and not that much more successful than CC-IUI. For all these reasons, FSH-IUI treatment will continue to be phased out.

REFERENCES

1. Lewis V, Queenan J, Hoeger K, et al. Clomiphene citrate monitoring for intrauterine insemination timing: a randomized trial. Fertil Steril 2006; 85:401–406.
2. Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine inseminations: analysis of more than 4100 cycles. Fertil Steril 2008; 90:2281–2286.
3. Haebe J, Martin J, Tekepety F, et al. Success of intrauterine insemination in women aged 40–42 years. Fertil Steril 2002; 78:29–33.
4. Harris ID, Missmer SA, Hornstein MD. Poor success of gonadotropin- induced controlled ovarian hyperstimulation and intrauterine insemination for older women. Fertil Steril 2010; 94:144–148.
5. Duran HE, Morshedi M, Kruger T, et al. Intrauterine insemination: a systematic review on determinants of success. Hum Reprod Update 2002; 8:373–384.
6. Polyzos NP, Tzioras S, Mauri D, et al. Double versus single intrauterine insemination for unexplained infertility: a meta-analysis of randomized trials. Fertil Steril 2010; 94:1261–1266.
7. Osuna C, Matorras R, Pijoan JL, et al. One versus two inseminations per cycle in intrauterine insemination with sperm from patients' husbands: a systematic review of the literature. Fertil Steril 2004; 82:17–24.
8. Bagis T, Haydardedeoglu B, Kilicdag EV, et al. Singe versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: a randomized trial. Hum Reprod 2010; 25:1684–1690.

8 Treatment options III. In vitro fertilization

Michael M Alper

In vitro fertilization (IVF) is one of the most significant advances in the field of reproductive medicine. The first IVF baby Louise Brown, born in England in 1978, was the result of a decade of research by Drs Patrick Steptoe and Robert Edwards. Since that time, over 400 IVF units have been established in the United States alone. Over three million babies have been born worldwide as a result of this technology and now around 1% of all babies born in the United States are conceived with IVF. Initially IVF was developed for the woman with tubal disease, but now it is the treatment of choice for other causes of infertility that are refractory to more conservative treatment. Since its introduction, all of the steps of IVF treatment have been improved upon which has resulted in continuously rising success rates over the last 20 years (Fig. 8.1). IVF is the most successful infertility treatment that can be offered. IVF has also provided a platform for the development of other treatments including egg donation, gestational surrogacy, and preimplantation diagnosis. This chapter provides an overview of the IVF treatment.

The following four steps of IVF are reviewed:

I. Ovulation induction
II. Oocyte retrieval
III. Oocyte insemination
IV. Embryo transfer

OVULATION INDUCTION

IVF treatment initially utilized nonmedicated or natural cycles. The timing of the egg retrieval was based on the initiation of the endogenous luteinizing hormone (LH) surge. Overall, the natural cycle and those cycles that used clomiphene citrate were extremely inefficient, and one of the first modifications that increased IVF success rates significantly was the use of gonadotropins to stimulate the growth of multiple ovarian follicles. This was a definite improvement, but premature ovulation complicated approximately 30% of cycles, making timing of the egg retrieval a challenge and cancellation common. The next breakthrough occurred in the late 1980s when the gonadotropin-releasing hormone (GnRH) agonist was introduced. The GnRH agonist eliminated any chance of a premature LH surge resulting in more control of the cycle. The ovulation induction step is extremely important since the success rate is directly related to the number of oocytes that are retrieved, which, in turn, impacts the number of embryos that are available for transfer. Over the years, there has been a change from the use of urinary gonadotropins to those preparations created by recombinant DNA technology. The newer gonadotropins are more purified allowing subcutaneous injection. The medications used for ovulation induction are listed in Table 8.1. The ovulation induction protocols that are used today are described below.

Pituitary Downregulation with a GnRH Agonist

Traditionally, pituitary downregulation has been the most common protocol utilized by IVF programs. Daily injections of a GnRH agonist, Lupron®, result in *downregulation* of pituitary GnRH receptors, which reduces pituitary follicle-stimulating hormone (FSH) and LH release and prevents an LH surge. Generally, the GnRH agonist must be administered for a period of 10 to 15 days before downregulation occurs. The quickest way to achieve downregulation is to start the GnRH agonist in the mid-luteal phase (cycle day 21) of the preceding cycle. It can also be started in the early follicular phase with the onset of menses. After downregulation has occurred, the dose of the GnRH agonist is reduced and the ovulation induction is initiated with FSH injections. The dose of FSH required may vary from 150 to 450 U/day.

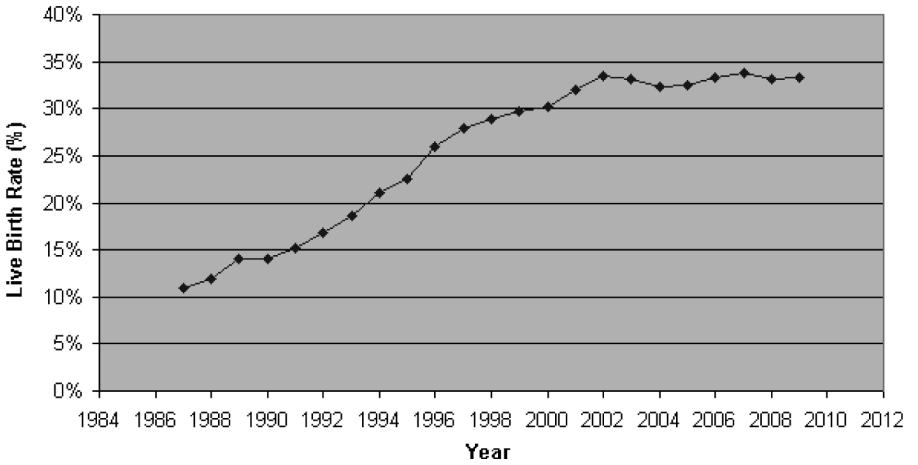

Figure 8.1 IVF treatment success rates have continued to increase. The live birth rate (per oocyte retrieval for all women treated during the calendar year) has increased threefold between 1987 and 2003 but since then success rates have plateaued. Data were obtained from the CDC/SART statistics that are published on an annual basis. The increase in the success rates has been paralleled by an increased number of ART procedures that have been performed in the United States. In 1987, a total of 8725 retrievals were performed and, in 2009, a total of 96,226 procedures were carried out. *Abbreviations*: IVF, in vitro fertilization; CDC/SART, Centers for Disease Control/ Society of the Assisted Reproductive Technologies; ART, assisted reproductive technology.

Table 8.1

Fertility Medications

Gonadotropin: Gonadotropins are injectable medications used for ovulation induction for intrauterine insemination and IVF treatment. Two types of gonadotropins can be administered and are discussed below:

1. FSH (Gonal-F®, Follistim®, Bravelle®): These medications contain only FSH and are administered by subcutaneous injection. These are the most commonly prescribed medications for ovulation induction.
2. Human menopausal gonadotropins (Menopur®, Repronex®): These medications contain equal amounts of FSH and LH, and are administered on a daily basis by subcutaneous injections.

GnRH agonist (Lupron®): This is a synthetic hormone that is administered by subcutaneous injection. The administration of a GnRH agonist initially causes release of FSH and LH from the pituitary gland. However, with continued administration there is downregulation of the GnRH receptors, which minimizes release of FSH and LH by pituitary gonadotrophs and prevents an LH surge. GnRH agonists are administered with gonadotropins in women undergoing IVF treatment. The main benefit is that pretreatment with a GnRH agonist prevents an LH surge.

GnRH antagonists (Ganirelix®, Cetrotide®): GnRH antagonists reversibly bind to GnRH receptors and prevent release of FSH and LH. The major benefit of the use of GnRH antagonists in conjunction with FSH is the suppression of the LH surge. In contrast to Lupron the GnRH antagonists have an immediate action in prevention of an LH surge.

Human chorionic gonadotropin (hCG) (Profasi®, Pregnyl®, Ovidrel®, Novarel®): This medication contains pregnancy hormone, hCG, which functions similarly to LH. LH is an important hormone that helps to mature the eggs to allow them to become fertilized and stimulates ovulation. The administration of hCG is necessary in women who are undergoing IUI (when gonadotropins are used) and during IVF treatment.

Progesterone supplements: Progesterone supplements are used in women undergoing IVF treatment to help prepare the endometrium for implantation and to support a pregnancy. Progesterone can be administered by intramuscular injection, vaginally and orally. Progesterone supplements are not FDA-approved for IVF treatment except for Crinone® and Endometrin® which are administered vaginally. However, the progesterone present in the supplements is the natural hormone and studies have confirmed there is no increased risk of congenital anomalies or health risks to women who take natural progesterone supplements during pregnancy.

Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; IVF, in vitro fertilization.

Microdose-Lupron

This protocol is used for women who are poor responders or who have evidence of reduced ovarian reserve. This protocol involves the administration of oral contraceptives for a period of three weeks. Theoretically, the administration of the oral contraceptives suppresses gonadotropin release and puts the ovaries to rest. After the three-week course of the oral contraceptives has been completed, small doses of Lupron and FSH are administered twice daily. When Lupron is administered in this fashion, it acts as a stimulatory agent because it induces the release of FSH and LH, and after continued administration there is inhibition of the LH surge.

Pituitary Suppression with a GnRH Antagonist

GnRH antagonists result in the immediate suppression of FSH and LH release from the pituitary gland, as opposed to agonists that take several days to suppress the pituitary. The use of GnRH antagonist protocols is becoming more popular. The advantages include fewer injections and elimination of the ovarian suppression that may occur after administration of Lupron. For this protocol, gonadotropins are started on cycle day 2. When a lead follicle reaches a diameter of 14 mm on transvaginal ultrasound examination, the daily administration of the GnRH antagonist is started (with the gonadotropins). The administration of the antagonist results in a decrease in the serum estradiol level in part because the antagonist completely eliminates all LH secretion. Some have advocated the addition of LH to compensate, but published data has failed to conclude that this is necessary.

Monitoring

During the ovarian stimulation, the woman's response is monitored with serum estradiol levels and vaginal ultrasound examinations. The estradiol level is used to determine the dose of gonadotropins and whether excessive stimulation is occurring. However, some studies have concluded that serum estradiol monitoring is not always necessary and the response to treatment can be followed with ultrasound monitoring alone. The goal of the ovulation induction is to develop at least three mature follicles that are 17 mm in diameter or larger. Once this is achieved, FSH and other medications are discontinued, and a single injection of human chorionic gonadotropin (hCG) is given to mature the eggs to allow fertilization. The hCG administration will also cause ovulation, but this does not occur until 40 hours or later following the injection. Therefore, it is standard that the hCG injection is administered 36 hours before the scheduled egg retrieval such that this will allow adequate maturation of the eggs and yet there is little risk of ovulation.

OOCYTE RETRIEVAL

The egg retrieval is performed under vaginal ultrasound guidance. First the vagina is cleansed with normal saline. Betadine is not used since it may be toxic to the eggs. The vaginal ultrasound is then placed in the vagina and the ovarian follicles are located. A 17-gauge needle is directed through the back wall of the vagina and directed into the ovarian follicles (Fig. 8.2). The fluid is aspirated and then examined by an embryologist to identify the microscopic egg (Fig. 8.3). All follicles within both ovaries are aspirated. Once the eggs are retrieved, they are placed in culture plates with nutrient media and then placed in the incubator. The procedure is performed under light anesthesia and generally takes less than 15 to 20 minutes to complete. Prophylactic antibiotics are routinely administered. The overall complication rate is $<1\%$.

OOCYTE INSEMINATION

Standard Insemination

After the sperm sample is produced, the sperm concentration and motility are assessed. If the sperm sample is adequate, then a sperm prep is done to isolate the most motile sperm. A total of 50,000 motile sperms are placed with the eggs in a culture dish, which is then placed in the incubator.

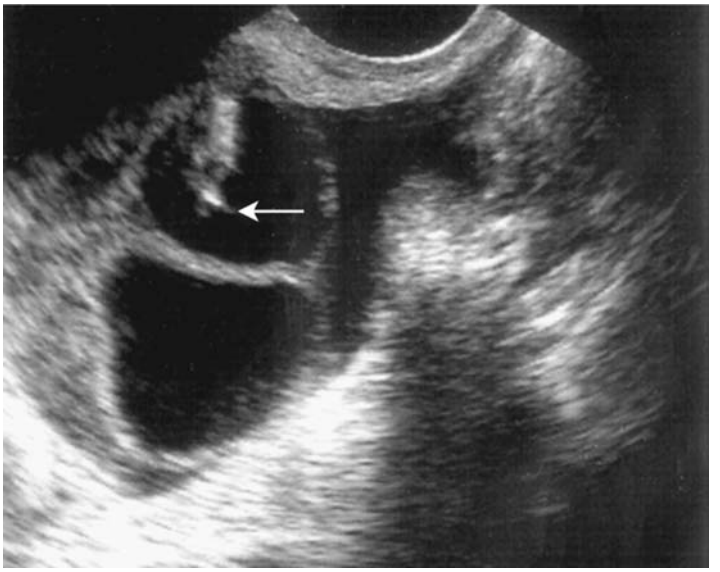

Figure 8.2 Vaginal ultrasound-guided egg retrieval. This is an ultrasound image taken at the time of egg retrieval. During the procedure, the ovary is positioned on the other side of the vaginal wall. A needle has been inserted through the vaginal wall, and the tip of the needle is positioned in the center of the follicle (*arrow*). After proper placement of the needle, the fluid from the follicle is aspirated.

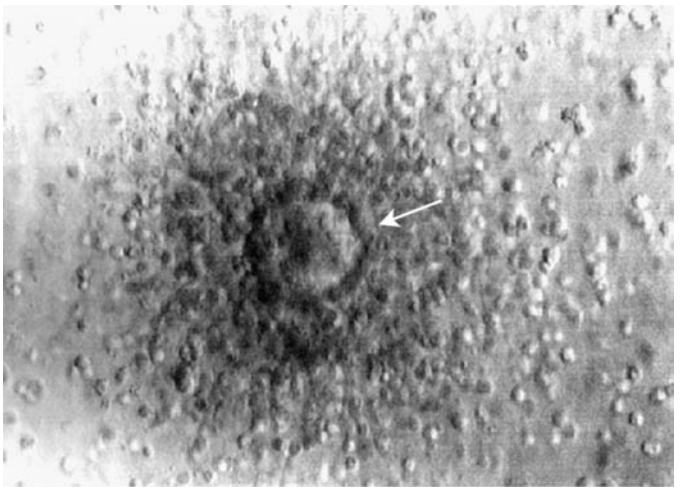

Figure 8.3 An oocyte. This picture is of an oocyte obtained at the time of egg retrieval. The oocyte (*arrow*) is surrounded by a group of granulosa cells called the cumulus oophorus. During normal fertilization, the acrosome of the sperm releases enzymes that disperse the cumulus cells therefore allowing the sperm to penetrate and fertilize the oocyte.

Intracytoplasmic Sperm Injection

Intracytoplasmic sperm injection (ICSI) is used in cases of male factor or in cases when a prior standard IVF resulted in <30% of eggs being fertilized. ICSI involves the injection of a single sperm directly into the oocyte (Fig. 8.4). In the United States, ICSI is used in 60% to 65% of IVF cycles. Fertilization rates following this procedure are between 60% and 70% (comparable to the rates achieved with a standard insemination). Males with severe oligospermia (count <5 million sperm/cc) should have a karyotype performed since they are at greater risk for having a chromosomal abnormality. Couples should be counseled that there is an increased risk of sex chromosomal anomalies in infants born following the ICSI procedure when it is performed in cases of severe oligospermia. The rate of sex chromosomal aneuploidy in infants conceived naturally is 0.2%, and is 0.8% following the ICSI procedure. These chromosomal abnormalities are not the result of the ICSI procedure itself but most likely due to the low

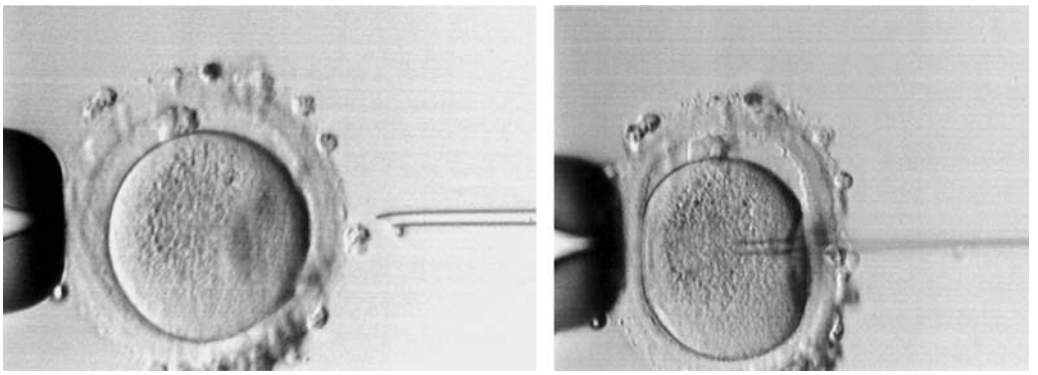

Figure 8.4 The ICSI procedure is performed with very fine instruments under a microscope. After the granulosa cells have been stripped away from the oocyte with enzymes, the oocyte is held in place by a holding pipette. The other pipette, which is much smaller and sharper, is used to pick up a single sperm. The smaller pipette is then brought into proper position (*left panel*) and then inserted through the zona pellucida and into the cytoplasm of the oocyte where the sperm is injected (*right panel*). *Abbreviation*: ICSI, intracytoplasmic sperm injection.

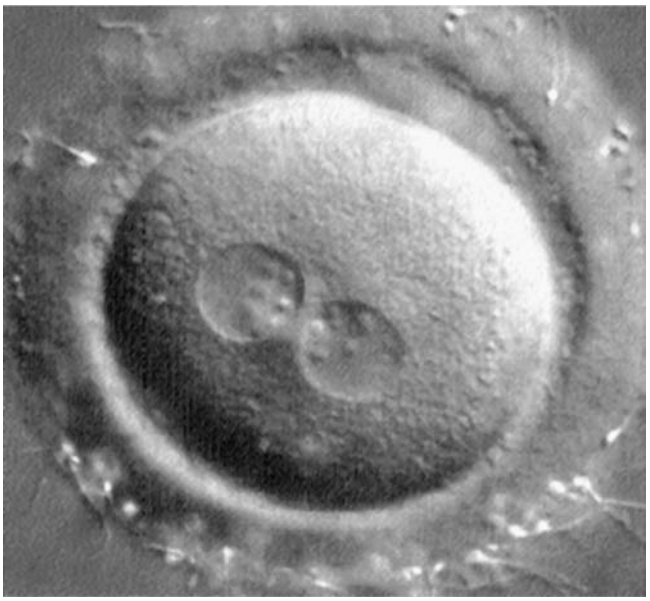

Figure 8.5 A fertilized egg. Note the two pronuclei (one from the sperm and one from the egg) present within the egg.

level of mosaicism present in the spermatogonia. Couples may opt for a genetic amniocentesis after pregnancy is established. Studies have confirmed that many cases of male factor infertility are caused by microdeletions on the Y chromosome. Couples should be counseled that this genetic testing is available and if a defect is found then it could be transmitted to a male offspring.

The morning after insemination, the eggs are examined to determine whether fertilization has occurred. A fertilized egg is shown in Figure 8.5. Note the two pronuclei (one from the sperm and the other from the egg) present within the egg. Within a few hours the nuclei unite and the embryo will start to divide.

EMBRYO TRANSFER

The embryo transfer can be performed either three or five days after the egg retrieval. There is a great deal of controversy regarding which is more optimal. On day 3, good-quality embryos are generally between six and eight cells (Fig. 8.6). To continue embryonic development in the laboratory from day 3 forward, a different culture media environment is needed. Commercially available culture media systems have been developed which allow the day 3 multicellular embryo to develop into a blastocyst on day 5. (Fig. 8.7) The advantage of waiting until day 5 is that it does provide additional time to select the better-quality embryos since only 50% to 60% of embryos have the ability to develop into blastocysts and therefore fewer embryos are transferred. However there are disadvantages of waiting until day 5. The blastocyst culture environment may not be optimal for all embryos, and freezing of extra blastocysts on day 5 is not as efficient as freezing extra multicellular embryos on day 3. Another disadvantage is that there is a higher chance of monozygotic twinning with a day 5 versus a day 3 transfer.

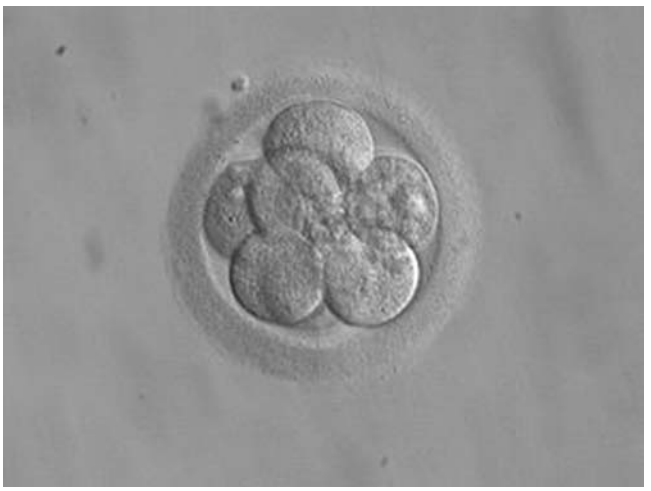

Figure 8.6 An eight-cell embryo. This state of development is achieved at approximately 48 hours after fertilization has been confirmed. Note the outer membrane called the *zona pellucida* that surrounds the embryo.

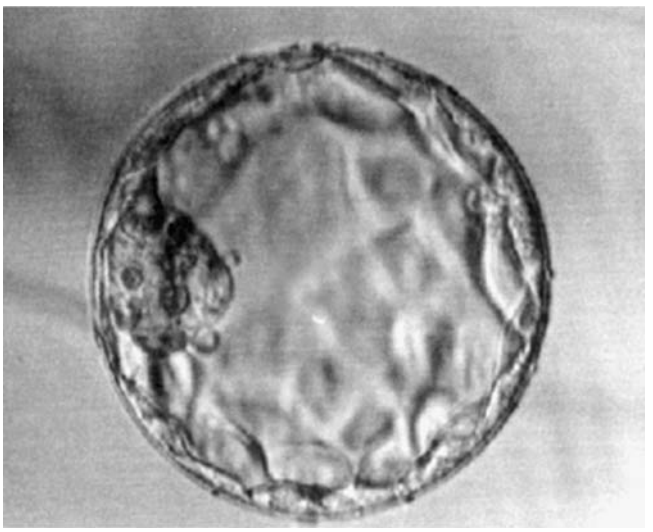

Figure 8.7 A blastocyst. Approximately 30% to 50% of embryos will develop to the blastocyst state five to six days after the egg retrieval. The blastocyst is made up of 50 to 100 cells.

Table 8.2 Boston IVF Recommended Embryo Transfer Guidelines

AGE (yr)	DAY 3	DAY 5
<35	1–2	1–2
35–38	2–3	1–2
39–40	3–4	2–3
41–44	4–5	2–3

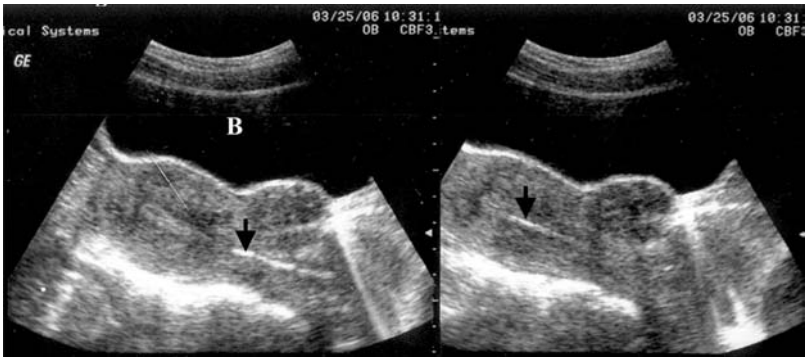

Figure 8.8 Ultrasound-guided embryo transfer. In the left panel, the filled bladder (B) allows adequate visualization of the uterine cavity. The tip of the catheter (*arrow*) has been advanced to the lower aspect of the uterine cavity. In the right panel, the catheter has been advanced to approximately 1.5 cm from the top of the cavity where the embryos are placed. A small anterior serosal fibroid can be seen slightly impinging on the bladder.

The recommended number of embryos to transfer is determined by the woman's age and the timing of the embryo transfer (Table 8.2). We perform the embryo transfer under abdominal ultrasound guidance. A full bladder creates a window so the uterus can be easily visualized. An echogenic catheter can be easily seen as it courses through the cervical canal and up into the cavity (Fig. 8.8). The catheter is positioned 1 to 2 cm from the top of the cavity where the embryos are placed. Extra embryos that are of satisfactory quality can be frozen and stored for future use. A serum pregnancy test is performed 11 days later.

Luteal Phase Support

Progesterone, a hormone produced by the ovary following ovulation, matures the lining of the uterus for implantation. Studies have shown that women who are undergoing IVF treatment need supplemental progesterone. For this reason, it is standard to administer progesterone following the egg retrieval. Natural progesterone is available and can be administered vaginally (Crinone®, Endometrin®, Prometrium®) or by intramuscular injection. If pregnancy occurs, the progesterone may be continued for a period of time. We generally continue the progesterone supplementation until fetal viability is confirmed. Studies have supported that there is no increased risk of birth defects or health risks to women who take natural progesterone supplements during pregnancy. In lieu of progesterone hCG injections (1500 U every 3 days × 3 doses beginning the day after the oocyte retrieval) can be administered in the luteal phase. However, hCG is rarely used to supplement the luteal phase due to the higher incidence of ovarian hyperstimulation syndrome.

IVF-Related Procedures

Frozen Embryo Transfer

Embryos that are cryopreserved during an IVF cycle can be replaced after a spontaneous ovulation (natural cycle) or the creation of an "*artificial*" endometrium with estrogen and progesterone. The success rate following this procedure is generally lower than the transfer of fresh embryos but dependent on the number and quality of embryos that are transferred. The main advantage of a frozen embryo transfer as compared to a medicated IVF cycle is that

ovulation induction drugs are not taken and, obviously, the oocyte retrieval is not performed. It is reassuring that there is no increased risk of congenital anomalies in infants born following the transfer of cryopreserved embryos.

Natural Cycle IVF

For couples who want to minimize the risk of a multiple pregnancy or would like to avoid the risks of the ovulation induction drugs, a natural cycle IVF approach can be considered. The woman undergoes monitoring with blood work and ultrasound examinations beginning on cycle day 10; hCG is administered when a mature follicle is identified. If an LH surge occurs, then the cycle must be canceled. The goal of the natural cycle approach is the retrieval of one egg and the replacement of one embryo. The success rate is much lower (<5%) than conventional IVF, which is a major disadvantage of this approach.

Gamete Intrafallopian Transfer

This treatment involves the first two steps of IVF treatment: ovulation induction and egg retrieval. In contrast to IVF, the gamete intrafallopian transfer (GIFT) procedure places the eggs and sperm in the fallopian tube, allowing the tube to be the natural incubator. Usually, four to six eggs are replaced. The disadvantage of the GIFT procedure is that a laparoscopy has to be performed under general anesthesia. A prerequisite to performing the GIFT procedure is that the woman must have at least one normal fallopian tube. This procedure was quite popular in the 1980s but is rarely performed nowadays due to the high success rates with IVF. Actually less than 1% of assisted reproductive technology (ART) procedures are GIFT. Indications for resorting to GIFT include altered cervical anatomy that prevents a successful uterine transfer, or preclusion of IVF due to religious reasons.

Tubal Embryo Transfer

This treatment involves the first three steps of IVF: ovulation induction, egg retrieval, and fertilization of the eggs in the laboratory. In contrast to IVF, the tubal embryo transfer (TET) procedure involves the laparoscopic placement of the embryos in the fallopian tube(s), allowing the tube to be the natural incubator. Usually, two to four embryos are replaced. The disadvantage of the TET procedure is that two separate procedures requiring anesthesia are performed, including the egg retrieval and a laparoscopy. This procedure is rarely performed but might be considered when there is altered cervical anatomy and the GIFT procedure is not an option (i.e., when the ICSI procedure is required).

Egg Donation

Egg donation can be considered for a woman who is a poor responder to the ovulation induction medications, has evidence of reduced ovarian reserve, or is a carrier of a genetic condition. All of the steps of IVF are performed except the egg donor undergoes the ovulation induction and egg retrieval. Once the eggs are retrieved, they are then fertilized with the recipient's husband's sperm. The recipient is treated with hormones including estrogen and progesterone, which create an endometrium that will allow implantation of the embryos. The donor can be anonymous or known (i.e., a relative, friend). Before this treatment is begun, all parties involved should undergo medical, psychological, and legal counseling. This topic is further discussed in the next chapter.

Gestational Surrogacy

Some women cannot carry a pregnancy but can produce eggs and embryos from IVF. Indications for gestational carrier treatment are when the woman has no uterus (e.g., prior hysterectomy), a congenitally deformed uterus, a uterus that is unable to support a pregnancy, or has a medical condition that precludes her from successfully carrying a pregnancy. All the steps of IVF treatment are performed except the embryos are transferred into a gestational carrier. Before this treatment is begun, all parties involved must undergo medical, psychological, and legal counseling.

Embryo Donation

When a couple decides that they do not want any more children or stop treatment, they must decide what to do with their frozen embryos. Because of religious or moral beliefs, some couples find it unacceptable to discard the embryos. One option is to donate the embryos to another couple. Embryo donation is just emerging as a treatment option for infertile couples and will be used more and more in the future. Embryo donation is very similar to adoption. Medical, psychological, and legal counseling are important components of the treatment.

Epididymal Sperm Aspiration

In some cases of azoospermia, sperm are being produced but do not find their way into the ejaculate. This may be the result of an obstruction (e.g., previous vasectomy, infection), congenital absence of the vas deferens, or in cases of severely impaired sperm production. In these cases, aspiration of epididymal sperm or testicular sperm by a urologist may be considered. In years past, the only way to aspirate epididymal sperm was via the microscopic epididymal sperm aspiration (MESA) procedure. This procedure is performed in the operating room under general anesthesia. More recently, the percutaneous epididymal sperm aspiration (PESA) procedure has become more popular. It can be accomplished under local anesthesia in the office with a much shorter recuperation than the MESA procedure. If epididymal sperm aspiration does not produce viable sperm, then the urologist can resort to testicular sperm extraction (TESE). In all cases of sperm aspiration, the motility of the sample is quite poor so the ICSI procedure must be performed. To accomplish this procedure, there must be coordination between the urologist and the IVF team. The sperm aspiration can be performed on the day of the oocyte recovery or prior to the IVF cycle and the samples frozen.

Laboratory Procedures

Assisted Hatching

Assisted hatching is a procedure in which the zona pellucida, the outer membrane surrounding the embryo, is thinned by either the application of a dilute acidic solution or more recently with a microscopic laser. It has been theorized that some implantation failures may result from failure of the embryo to hatch out from the confines of the zona pellucida. However, published studies are inconclusive about the benefit of this procedure. Therefore, it should not be used universally but might be considered in patients who have undergone several IVF cycles that have been unsuccessful or in older women.

Preimplantation Genetic Diagnosis

In the past when a couple was at risk of having a child with a genetic condition, the only options for genetic diagnosis were a chorionic villous sampling or a genetic amniocentesis. These choices are not optimal since terminating a pregnancy can be quite stressful and for many couples is not considered an option. Preimplantation genetic diagnosis (PGD) provides couples with another option. The refinement of micromanipulation techniques has provided the ability to perform genetic diagnosis on a single blastomere that is removed from the embryo prior to transfer. The first successful case of PGD was performed in 1990 for a couple who were at risk of having a child with cystic fibrosis. Since that time, centers worldwide have developed the expertise to perform PGD. It can be performed for autosomal recessive and dominant conditions, to assess aneuploidy and for translocations. PGD is an emerging technology, and as more and more genetic probes become available, there will be an increased demand for this procedure.

Oocyte Freezing

Oocyte freezing is another emerging technology. The oocyte, in contrast to the embryo, is quite sensitive to the cryopreservation process. This is related to the high water content in the egg, which predisposes it to ice crystal damage. Recently, breakthroughs have been made in the technique resulting in improved survival at the time of thawing. There are two main laboratory methods to freeze human eggs: (1) Slow freezing which involves gradual freezing in a

programmable freezer, and (2) Fast freezing (vitrification) in which the eggs are frozen very rapidly. It is anticipated that egg freezing will become more available for routine clinical use. The indications for oocyte freezing are many fold. It gives opportunity to women undergoing cancer treatment to preserve fertility. It also would benefit the younger woman who doesn't anticipate motherhood in the near future and wants to preserve her fertility. Finally, couples undergoing IVF could freeze extra eggs instead of embryos. Once the couple decides that their family is complete it is much easier emotionally to discard frozen eggs instead of frozen embryos.

Success Rates

IVF success rates continue to improve and the reasons are many fold, including improved ovulation induction medications, refined laboratory techniques, less traumatic embryo transfer catheters, and the introduction of the ICSI procedure. The success rate for any individual patient following IVF is influenced by countless factors including the number of embryos transferred, cycle number, ovarian reserve, age, and diagnosis. Center-specific data is difficult to compare due to the variation in patient selection and philosophy regarding treatment.

Maternal Age

One of the most important factors that influence a couple's fertility is the woman's age. Generally, younger women have a greater quantity and quality of eggs that once fertilized are more likely to implant in the uterus and result in a pregnancy. Furthermore, the chance of a miscarriage is lower in younger women. The decreased fertility associated with advancing age is a gradual process that seems to begin around age 35 and then accelerates after the age of 40. One reason for the decreased fertility associated with aging is that there is a higher rate of aneuploidy. Women over the age of 40 should be counseled about the decreased chances of pregnancy even with aggressive treatment, such as IVF (Fig. 8.9). Treatment is inadvisable in women who are 44 years and older because of the dismal chance of a successful outcome. These women should be counseled and encouraged to pursue other more successful options such as egg donation and adoption.

Diagnosis

Women with ovulatory problems, except those with reduced ovarian reserve, tend to have higher pregnancy rates with the various treatments. Women with tubal factor infertility or severe male factor infertility seem to fare poorly with conservative interventions (i.e., ovulation induction with or without intrauterine inseminations). While the cause of the infertility may impact on the success of conservative treatments there is virtually little difference between the success rates for the different diagnostic categories with IVF treatment (Fig. 8.10).

Fertility Clinic Success Rate and Certification Act of 1992

Since the passage of the Fertility Clinic Success Rate and Certification Act of 1992, it is mandatory that all IVF centers in the United States submit their annual success rates to a federal registry. In the past, this was a joint venture of the U.S. Centers for Disease Control (CDC) and the Society of the Assisted Reproductive Technologies (SART), a subsidiary of the American Society for Reproductive Medicine (ASRM). After the annual data have been compiled, a finalized report is published and made available to the public for review. The published document includes a summary of national and clinic-specific success rates. The main impetus behind this law is that the reporting of clinic success rates would help the infertile couple select the *best* IVF clinic for their treatment. Unfortunately, there are several shortcomings to this process. Because the published data are based on live birth rates, the most recent data that have been published are two to three years old and may not reflect a clinic's current success rate. Another pitfall to the interpretation of the data is that there is no way to decipher the inclusion and exclusion criteria that any individual center used in selecting patients for treatment. Therefore, as these criteria are highly variable for each program, center-by-center comparison of success rates is not valid. Some highly experienced IVF programs attract more difficult cases that cause their statistics to be lower. Therefore, it is important for patients to not use the CDC statistics to choose an IVF program. What is more important is to determine an individual's chance of success within a particular program. An unfortunate outcome to the process is that some IVF centers have used the published data for marketing

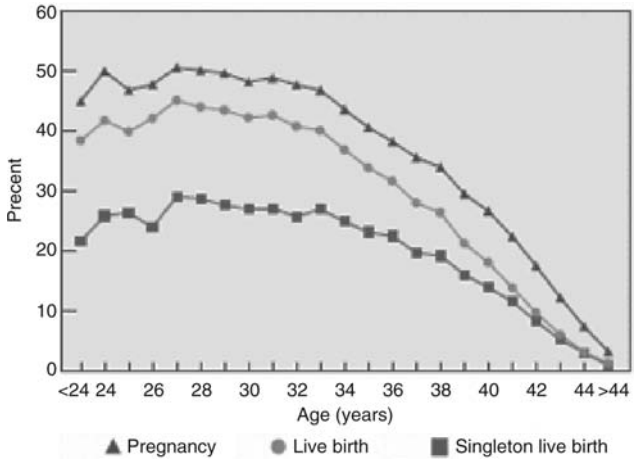

Figure 8.9 Pregnancy and live birth rates for ART cycles using fresh (nondonor) embryos by age of the woman. *Abbreviation*: ART, assisted reproductive technology. *Source*: From Ref. 1.

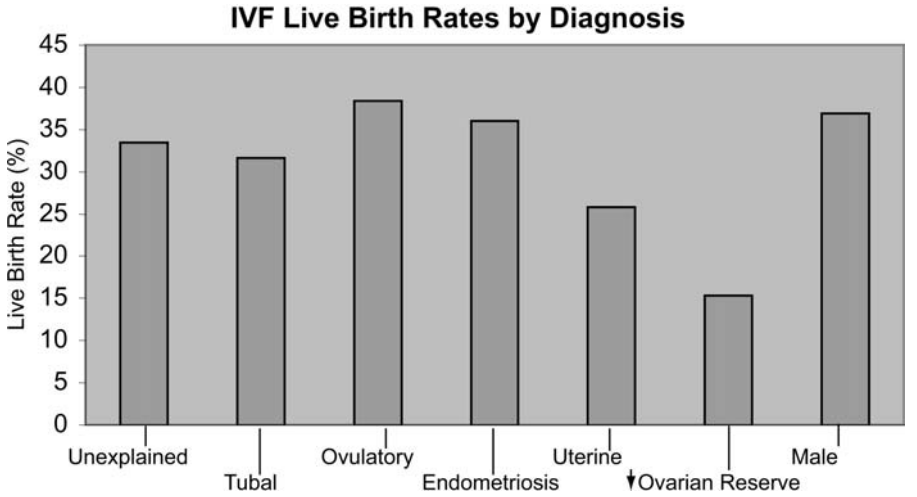

Figure 8.10 Live birth rates following IVF by primary diagnosis. *Source*: From Ref. 2.

purposes. Despite these shortcomings, a major benefit of the data collection is to follow national trends and success rates of the various ART procedures. The CDC ART statistics can be viewed online. Data extracted from the 2009 National ART Summary report is presented in Table 8.3.

Table 8.3 2009 Live Birth Rates (Per Cycle Initiated) by Age Group for Various IVF Procedures

	Live birth rates by age group (%)					
Treatment	<35 yr	35–37 yr	38–40 yr	41–42 yr	>42 yr	Multiple pregnancy rate
IVF (± ICSI)[a]	41.4	31.7	22.3	12.6	4.2	29[b]
Frozen embryo transfer[c]	35.6	30.9	26.1	22.1	13.9	
Egg donation[c]			55.1			

[a]Live birth rates per cycle initiated.
[b]Multiple pregnancy rate: twins, 27.5%; triplets and more, 1.4%.
[c]Live birth rates per embryo transfer.
Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

Complications of Treatment

Multiple Pregnancy

Most multiple pregnancies following IVF treatment result from the implantation of more than one embryo. Therefore, the chance of a multiple pregnancy increases with the number of embryos that are transferred. In the most recently published CDC/SART report, the percentage of pregnancies delivered that were twins was approximately 28% and triplets 1–2%. Multiple pregnancies are associated with an increased risk of most complications of pregnancy including miscarriage, toxemia, congenital anomalies, gestational diabetes, and premature birth. The most concerning risk of a multiple pregnancy is prematurity. Babies born from a triplet pregnancy have a 20% chance of a major handicap, 17-fold increase in cerebral palsy, and 20-fold increase in death during the first year after birth (as compared to a singleton pregnancy) (3). Monozygotic twinning (MZT) is a multiple pregnancy that results from the splitting of a single embryo, which will lead to a set of identical twins. The incidence of MZT is increased in pregnancies conceived following IVF. The incidence of MZT is 1% following a day 3 transfer and 3-4% following a day 5 transfer. MZT pregnancies are more complicated due to the risks of twin-to-twin transfusion and cord accidents. A multiple pregnancy may also pose increased emotional and financial hardship for a couple. If a multiple pregnancy develops, the couple may consider a multifetal reduction procedure. This procedure, which is performed in the first trimester of pregnancy, reduces the number of fetuses to a lower and safer number. Although the success rate is 90% to 95%, a miscarriage may result from the procedure.

During the early 1990s, there was a progressive increase in the number of triplet pregnancies. Since 1997, there has been a plateau in the number of high-order multiple pregnancies. In the 1990s, there was a concerted effort from the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine to develop guidelines to help reduce the number of embryos transferred (4,5). In addition, the continued progress in the field has produced higher implantation rates, which also has provided a further impetus to reduce the number of embryos transferred without impacting on pregnancy rates (6). With the continued improvement in outcomes there is not now consideration to transferring a single embryo in selected cases.

Birth Defects

The possibility that IVF could increase the risk of birth defects has been a great concern for patients and clinicians. This is of particular interest since about 1% of all children are now conceived following IVF. Although many studies have looked at malformations in IVF children, most have had limitations in sample size and there has been a lack of a standard definition of a minor versus a major congenital malformation. However, the majority of studies point to a slightly increased risk of congenital malformations. A previous meta-analysis including seven studies compared the rate of birth defects between those conceived following ART (IVF and ICSI) with those naturally conceived (7). The pooled odds ratio was 1.40 (95% CI 1.28–1.53) and confirmed an increased risk of major birth defects in the babies conceived by ART. In a recent case-control study, the researchers confirmed a higher incidence in singleton IVF pregnancies of septal heart defects, cleft lip/palate, esophageal atresia, and anorectal atresia (8).

The explanation for the increased risk of malformations is unclear but, may be the result of some aspect of the treatment itself or genetic factors in the couple undergoing the treatment. A major deficiency of most studies is that they do not include babies born to infertile women who were not treated by IVF—this is unfortunate since it is well known that congenital malformations are more common in the infertile population. ICSI does not appear to increase the rate of malformations in comparison to standard insemination technique (9,10). The transfer of previously cryopreserved embryos does not convey a higher rate of malformations in comparison to the transfer of fresh embryos (11,12). In conclusion, infertile women are at greater risk of having a baby born with a congenital malformation whether they conceive spontaneously or following treatment.

It is unclear whether there is an increased risk following IVF itself but, if so, the overall risk is still low when one considers the baseline major malformation rate, which is 3% in the United States. This information needs to be conveyed to our patients and should be part of the informed consent process. We counsel our couples that the incidence of birth defects in naturally conceived pregnancies is 2% to 3% and may be increased to 3% to 4% in babies born following IVF treatment.

Ovarian Hyperstimulation

Ovarian hyperstimulation syndrome (OHSS) can be a complication following the use of any ovulation induction agent but is more common following the use of injectable medications. It is a clinical situation whereby cysts develop in the ovaries following hCG administration. The symptoms that occur depend on the number and sizes of the cysts that are present. Patients at risk for OHSS are those with polycystic ovary syndrome (PCOS), high estradiol levels, and those with many smaller follicles (<12 mm) at the time of the hCG. However, most patients who develop OHSS don't have any risk factors. The timing of the development of symptoms is generally 7 to 10 days after the hCG administration. Over half of cases of OHSS are brought on by the rising β-hCG levels during the early stages of pregnancy. Approximately 20% to 30% of IVF patients develop mild OHSS and their symptoms include mild lower abdominal discomfort and distention. The symptoms are self-limited and resolve in a week. Approximately 1% to 2% of women who undergo IVF develop symptoms compatible with severe OHSS. The abdominal pain and distention is more significant and can be accompanied by the development of shortness of breath (SOB), nausea, vomiting, and decreased urine output. With severe OHSS there is accumulation of ascitic fluid that via the lymphatics can traverse into the pleural spaces. With the accumulation of ascites there can be contraction of intravascular volume with resultant hemoconcentration that can lead to thrombotic events resulting in stroke, kidney damage, and possibly death.

Management

All patients should be educated on the symptoms of OHSS. Any patient who develops symptoms of OHSS must be evaluated. If the symptoms are mild, then the patient is instructed to take daily weights and maintain oral fluids. The patient is called on a daily basis to be assessed. If she increases her weight by 2 or more pounds, has worsening pain, or develops SOB she is brought in for an evaluation. A physical exam is performed along with vital signs. The presence of tachycardia can be a sign of contraction of the intravascular volume which can occur with acute ascites. On the lung exam, reduced breath sounds at the bases can be a sign of a pleural effusion. A gentle abdominal exam will provide an idea as to the severity of the ascites. A pelvic exam is not performed since the ovarian cysts are prone to rupture. A vaginal and abdominal ultrasound exam will delineate the extent of the ascites. Laboratory studies are obtained including a CBC, PT/PTT, and electrolytes. The result of the CBC is most important and will give an idea of the degree of the hemoconcentration. If the hematocrit is >48% then prophylactic anticoagulation is administered (Lovenox 40 mg qd) until the syndrome resolves.

Traditionally, the treatment for severe OHSS was hospitalization with fluid restriction and careful fluid management. IV albumin was administered to mobilize the fluids. Our present management is to perform a vaginal ultrasound-guided paracentesis to remove the ascites (13). Indications to perform a vaginal paracentesis include severe pain, SOB, or evidence of hemoconcentration. We have found that this approach speeds up the recovery and resolution of the OHSS. We have removed up to 3 liters of fluid without any difficulty. This approach has essentially eliminated the need for hospitalization. (14).

Ovarian Cancer

In the general population, every woman has a 1 in 70 chance of developing ovarian cancer during her lifetime. Known risk factors for ovarian cancer include infertility, nulliparity, and genetics. Alternatively, birth control pill use and pregnancy reduce a woman's lifetime risk of developing ovarian cancer. It has been theorized that the number of ovulations that occur during a woman's lifetime increases the chance of cancer formation. Hence, there is concern that

the use of fertility medications could heighten the risk. This topic has been studied extensively. The Danish cohort of 50,000 infertile patients is the largest study to date that helped to shed light on the topic. The investigators in the initial study reported a higher incidence of breast and ovarian cancer in the infertile population (15). In a follow-up study of the cohort, the investigators sought to determine the impact of fertility medications on the risk of ovarian cancer (16). They concluded that the incidence of ovarian cancer was not increased in those infertile women who took fertility medications. These findings were supported by a recent review by Brinton et al. (17). Therefore, while it is fact that infertile women are at greater risk of developing ovarian cancer, this risk is not heightened with the use of fertility medications.

REFERENCES

1. Centers for Disease Control. 2008 Assisted Reproductive Technology Success Rates. Available at: http://www.cdc.gov/art/ART2008/sect2_fig6-15.htm#15.
2. Centers for Disease Control. 2008 Assisted Reproductive Technology Success Rates. Available at: http://www.cdc.gov/art/ART2008/sect2_fig16-26.htm#f21.
3. American College of Obstetricians and Gynecologists. Clinical Management Guideline for Obstetricians and Gynecologists. Multiple gestation: complicated twin, triplet and high order multifetal pregnancy. ACOG Practice Bulletin, Number 56, October 2004.
4. American Society for Reproductive Medicine. Guidelines on number of embryos transferred. A Practice Committee Report-A committee Opinion. (Revised). American Society for Reproductive Medicine, 1999.
5. American College of Obstetricians and Gynecologists. Nonselective embryo reduction: Ethical guidance for the obstetrician-gynecologist ACOG Committee Opinion 215. Washington: American College of Obstetricians and Gynecologists, 1999.
6. Tepleton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. N Engl J Med 1998; 339(9):573–577.
7. Hansen M, Bower C, Milne E, et al. Assisted reproductive technologies and the risk of birth defects—a systematic review. Hum Reprod 2005; 20:328–338.
8. Reefhuis J, Honein MA, Schieve LA, et al. Assisted reproductive technology and major structural birth defects in the United States. Hum Reprod 2009; 24:360–366.
9. Bonduelle M, Liebaers I, Deketalaere V, et al. Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999). Hum Reprod 2002; 17:671–694.
10. Palermo GD, Colombero LT, Schattman GI, et al. Evolution of pregnancies and initial follow-up of newborns delivered after intracytoplasmic sperm injection. JAMA 1996; 276:1893–1897.
11. Wennerholm UB, Albertsson-Wikland K, Bergh C, et al. Postnatal growth and health in children born after cryopreservation as embryos. Lancet 1998; 351:1085–1090.
12. Wada I, Macnamee MC, Wick K, et al. Birth characteristics and perinatal outcome of babies conceived from cryopreserved embryos. Hum Reprod 1994; 9:543–546.
13. Alper MM, Smith L Sills ES. Ovarian hyperstimulation syndrome: current views on pathophysiology, risk factors, prevention, and management. J Exp Clin Assist Reprod 2009; 6:3.
14. Smith LP, Hacker MR, Alper MM. Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. Fertil Steril 2009; 92(6):1953–1959.
15. Jensen A, Sharif H, Olsen J, et al. Risk of breast cancer and gynecologic cancers in a large population of nearly 50,000 infertile Danish women. Am J Epidemiol 2009; 168:49–57.
16. Jensen A, Sharif H, Frederiksen K, et al. Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study. BMJ 2009; 338:1–8.
17. Brinton LA, Moghissi KS, Scoccia B, et al. Ovulation induction and cancer risk. Fertil Steril 2005; 83:261–274.

9 Treatment options IV. Third party reproduction

Brian M Berger

Over the past 30 years, the use of assisted reproductive technologies (ART) has changed the choices available for older women. These choices include donor egg in vitro fertilization (DE IVF), which is now a standard treatment in most IVF centers. Patients who would benefit from DE IVF include women with premature ovarian failure, ovarian failure due to either chemotherapy or radiation, and women with gonadal dysgenesis. A second and much larger group includes women with diminished ovarian function and age-related infertility. Other candidates include women who have previously failed multiple IVF attempts and women carrying transmittable genetic abnormalities that could affect their offspring.

INCREASING NUMBER OF DE IVF CYCLES

There are many reasons for the recent increase in the number of women who are candidates for egg donation, such as patients with diminished ovarian function. Surveys have shown that many couples prefer to delay childbearing and rear their children only after establishing a stable relationship and financial security. There are also increasing numbers of late and second marriages and more women now wish to finish their education and establish a career before trying to start a family (1). In 2008, 436 programs reported use of donor oocytes to the American Society for Reproductive Medicine (ASRM)/Society for Assisted Reproductive Technology Registry. Donor eggs or embryos were used in approximately 12% of all ART cycles performed (18,121 cycles), and among the 6843 pregnancies that resulted from ART cycles using fresh embryos from donor eggs, approximately 52% were singleton pregnancies, 39% were twins, and more than 3% were triplets or more (2,3). The overall DE live birth rate using fresh and frozen embryos was 55% and 33%, respectively.

ETHICS OF DE IVF

Several publications have addressed the important ethical considerations and social issues related to egg donation in postmenopausal women. Generally, there are three main objections related to this treatment: (*i*) the physical risk to the older woman during pregnancy (4); (*ii*) the rights of the children born to older women (5); and (*iii*) the use of scarce health care resources that might deprive younger patients of treatment. Other issues that have been raised against treating older patients include the views of donors about using their oocytes for treating older women, and the psychological effect of giving birth beyond the age of 50, which is unknown at present (4). Those who are in favor of treating older patients argue that, by careful selection of patients, the risk of complications is reduced to a minimum and most older women wanting children are quite willing to accept the small risk of complications. There is also argument about the definition of what constitutes advanced maternal age, especially given the fact that the life expectancy of both men and women has increased very considerably (6).

STEPS TO COMPLETING A CYCLE OF DE IVF

The process of completing a DE IVF cycle has five distinct steps (Table 9.1). The patients are instructed to first set up an appointment with their physician to discuss the medical aspects of DE IVF. Spouses or partners must accompany the recipient to this appointment.

THE DONOR EGG TEAM

At Boston IVF we have a designated DE team that is responsible for working with all recipients to ensure that the recipient and her partner (if applicable) and the egg donor have been properly screened, and for synchronizing and coordinating the recipient's and donor's menstrual cycle. The recipients are instructed to attend an Egg Recipient Seminar with the egg donation program coordinator. At this seminar, comprehensive information about egg donation is given and all questions regarding the process are answered. We also have the

Table 9.1 Five Steps to Completing a Donor Egg Cycle

Responsible party	Steps
IVF center	Completion of the recipient eligibility screening process
Recipient/IVF center	Determination of insurance eligibility/financial clearance
Recipient	Selection or identification of a potential donor
IVF center	Screening of the potential donor
IVF center	Cycle coordination

patients meet with the financial coordinator. Depending on the patient's circumstances, they learn about what their insurance policy may cover, discover what testing may be required by the insurance company, and lastly, discover what their out-of-pocket costs will be. Egg donation treatment has become expensive and the charges including the IVF cycle, payment to the donor and agency, and costs of screening can total up to $30,000 to $40,000. Overall costs will be reduced if the couple uses a known egg donor.

FDA REGULATIONS AND EGG DONATION

The Food and Drug Administration (FDA) has published the final rules to strengthen regulation of human tissue, and expanded the regulations to include human cells, tissues, and cellular and tissue-based products (7). The new regulations apply to reproductive tissues such as eggs, embryos, and semen. The FDA began requiring various establishments to register with the agency and list the products manufactured starting on March 29, 2004. These establishments include those that recover, process, store, label, package, or distribute the products, or that screen or test their donors. More than 350 reproductive establishments, including semen banks and fertility clinics, have registered with the FDA.

Reproductive establishments including IVF centers were required to comply with donor eligibility requirements, which became effective on May 25, 2005. These requirements establish screening and testing criteria for donors of human cells, tissues, and cellular and tissue-based products to help prevent the transmission of communicable diseases. People who are donating to their own sexual partners are not required to be screened or tested.

For egg donors, the collection of a donor specimen for testing must occur up to 30 days before recovery of the oocytes or egg retrieval (8) (Table 9.2). For sperm donors (fresh specimen), the center may collect the donor specimen up to seven days before or after the sperm is donated (8) (Table 9.3).

Table 9.2 FDA Required Testing for Communicable Disease Agents or Diseases in Oocyte Donors

- Human immunodeficiency virus (HIV), types 1 and 2
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- *Treponema pallidum* (syphilis)
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*

Source: From Ref. 7.

Table 9.3 FDA Required Testing for Communicable Disease Agents or Diseases for Sperm Donors

- Human immunodeficiency virus (HIV), types 1 and 2
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- *Treponema pallidum* (syphilis)
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Human T-lymphotropic virus, types 1 and 2
- Cytomegalovirus

Source: From Ref. 7.

Required testing must be performed by an FDA-certified laboratory. Centers must also use an appropriate FDA-licensed, approved, or cleared donor screening test if available. A donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test may nevertheless be considered eligible, as long as all other required testing and screening are negative. A donor whose specimen tests reactive on a treponemal confirmatory test is not eligible.

THE EGG RECIPIENT EVALUATION

All recipients are tested according to FDA regulations as described above. In addition, if recipients have not already done so, we require a recent (within 6 months) uterine cavity evaluation; this can be accomplished with a hysterosalpingogram, sonohysterogram, or hysteroscopic examination of the uterine cavity. Recipients are instructed to once again schedule an appointment with their physician who will review the results of the recipient evaluation and write orders for the cycle.

All recipients are required to schedule an appointment with a social worker. Once again, the spouse/partner must attend this appointment. This consultation allows them to explore the psychological issues involved in egg donation. If recipients are working with an egg donor who is known by or related to them (known donor or KD), we require that they meet once with a social worker as a couple, the donor and her spouse (if applicable) meet with the social worker once as a couple, and then all four meet again for a joint consultation.

To prevent miscommunication and confusion, we only allow the screening of one potential egg donor at a time. Recipients are also told that they are financially responsible for services rendered to the donor, even if she is not accepted as a donor following her medical screening.

DONOR EGG AGENCIES AND ANONYMOUS DONORS

Boston IVF allows anonymous donors to be recruited by approved egg donor agencies *only*. We will not permit recipients to recruit their own donors through the Internet or through any other means. This policy is necessary to ensure that anonymity is preserved and that the necessary legal contracts are properly in place. Recipients are given tremendous guidance in selecting an appropriate egg donor (Table 9.4).

Table 9.4 Features to Seek in a Donor Egg Agency

Qualities	Importance
Medical expertise	An agency that offers a staff member with medical training is invaluable. Medical expertise is important to make decisions about which donors the agency will accept and make available to recipients.
One rate of compensation for every donor	The compensation provided to an egg donor is not a payment for her eggs. It is compensation for her inconvenience, time, effort, discomfort, and the medical risk that she assumes. Agencies that offer an elite class of egg donor, or who allow donors to choose their own fees, are taking advantage of recipients who are willing to pay for certain personal characteristics like a commodity. This practice is considered unethical and is discouraged by the American Society for Reproductive Medicine. (See above.)
Legal counsel for both the donor and recipient	Legal consultation for both the donor and the recipient protects the interests of both parties by establishing a mutually acceptable legal contract. An agency should facilitate this process and should provide this service as a part of the agency package.
Short-term medical insurance policy for the egg donor	Should an egg donor experience any adverse medical event related to the egg retrieval or the medications, the recipient is financially responsible for her medical care and treatment. A good agency should offer for purchase a short-term insurance policy that covers any potential problems related to the procedure and the medications.
Professional, courteous staff	A staff that is professional and courteous will treat egg donors and recipients with respect and ensure that the needs of each are met in an efficient manner. Professional demeanor usually reflects a company that is organized and efficient.

Egg donors should be healthy, between the ages of 21 and 35 (9,10), and free of infectious diseases. All egg donors, whether anonymous or known, must be screened to ensure that their motivation appears reasonable and voluntary. Egg donation presents a number of unique medical, legal, and emotional issues that need to be carefully considered.

APPROVED AGENCIES

According to guidelines published by the ASRM, programs recruiting oocyte donors and those assisting couples that have recruited their own donors should establish a level of compensation that minimizes the possibility of undue inducement of donors and the suggestion that payment is for the oocytes themselves: "To avoid putting a price on human gametes or selectively valuing particular human traits, compensation should not vary according to the number or quality of oocytes retrieved or the donor's ethnic or other personal characteristics" (11). Boston IVF adheres to these guidelines and will not work with agencies that are in direct violation of the ASRM guidelines.

KNOWN EGG DONORS

Known egg donors include sisters, relatives, friends, or colleagues. Known egg donors must be medically and psychologically screened as rigorously as anonymous donors. Cross-generation egg donation in which a daughter donates to her mother or a mother donates to her daughter is not permitted at Boston IVF.

LEGAL CONTRACTS

We require legal consultation and establishment of a legal contract with the donor, anonymous or known. The recipient couple is generally responsible for legal fees incurred by the donor, although many donor egg agencies include this fee in their administrative fees.

INITIATING THE TREATMENT CYCLE

When recipients have selected a potential donor, the agency (or recipient if using a known donor) calls the Egg Donation Program Coordinator who will mail them application and history forms, register the donor at Boston IVF, and schedule the donor's appointments. The donor should bring her completed forms and any previous medical records with her to her appointments. If using an agency, it is important for recipients to find out all of the costs of the agency before selecting an agency or paying a fee. Agency fees typically include the egg donor's compensation, a short-term medical insurance policy for the egg donor, and legal fees. In addition, if they select a donor who lives out of state, we require that she travels to Boston IVF twice: once for her screening appointments, and again for the monitoring and egg retrieval. At the time of the egg retrieval she usually stays locally for one week.

SCREENING DONORS

Boston IVF screens potential egg donors thoroughly according to FDA regulations. An 8-page phone screen is first performed and a decision is made on whether or not to schedule a screening appointment. The Boston IVF physician, social worker, and the DE program coordinator work as a team to determine whether a donor candidate is appropriate. We perform a karyotype and genetic testing on all donors (Table 9.5). If donors belong to certain ethnic groups, such as African-American, Ashkenazi Jewish, Mediterranean, etc., they are screened for additional genetic tests that apply. If a donor completes her screening and is approved by the medical director, the DE program coordinator is responsible for synchronizing the recipient's cycle with the egg donor's cycle.

Table 9.5 Genetic Testing on All Donors

- Karyotype
- Cystic fibrosis
- Fragile X
- Hemoglobin electrophoresis

CYCLE COORDINATION

Donors

Implantation and Success in DE IVF

The process of implantation remains poorly understood, but two factors are clearly required: endometrial receptivity and synchronization of embryo and endometrial development. In the natural cycle, these factors are induced by the simultaneous development of the follicle and the hormonal events surrounding ovulation. In the DE IVF treatment, these events are, by definition, separated and need to be controlled and synchronized by a sequence of ovarian downregulation and endometrial preparation. Because of these factors, controlled timing of follicle growth and egg maturation and ovulation in the donor and adequate stimulation of the endometrium with an estrogen-progesterone sequence in the recipient needs to be performed.

Donor Ovulation Induction Protocol

All donors are initially started on oral contraceptive pills (OCP). The OCP is started with the donor's menses and continues for 16 to 35 days. OCP pretreatment in high responders has been shown to improve the success of the treatment and also reduce the risk of ovarian hyperstimulation syndrome (OHSS) (12). The OCP is stopped on a Monday and the donor is instructed to call with the first day of her withdrawal bleed. Gonadotropin stimulation is then started the following Saturday. This regimen assures that the egg retrieval will most often occur in the middle of the week (13).

For several years, we have used a regimen consisting of follicle-stimulating hormone (FSH)/leutinizing hormone (LH) and a gonadotropin-releasing hormone (GnRH) antagonist (Table 9.6). This protocol allows us maximum flexibility in treatment and also has allowed us to almost eliminate the incidence of ovarian hyperstimulation (<0.2%) (14). We perform frequent estradiol (E2) measurement in the beginning of the cycle in order to adjust the stimulation and also to ensure that the donor is responding adequately (Table 9.7). We have also successfully utilized a protocol in which early adjustments in FSH dose are implemented based on the estradiol measurement on days 3 and 5 (15). We have found that modification of the initial and subsequent recombinant human follicle-stimulating hormone (r-hFSH) dose yields similar

Table 9.6 Donor Ovulation Induction Protocol

Medication Regimen:

- OCP start date: _____
- OCP stop date **Monday*:** _____
- Start FSH/Luveris on **Saturday**:** _____
- FSH dose 225 units/ 75 Luveris® QD x 2 days or
- FSH dose _____ units/ _____ Luveris® QD x 2 days

Antagonist

With lead follicle ≥ 14mm:

- Cetrotide 0.25 mg sc QD _____
- Ganirelix 0.25 mg sc QD _____

*Stop OCP on Monday, start FSH/Luveris on Saturday
**If menses on Tues/Wed, begin FSH/Luveris on Friday

Table 9.7 Monitoring Protocol for Donors

- E2 only on stimulation day 3 and day 5
- Ultrasound only after stimulation day 5
- On stimulation day 3 if E2 > 150, decrease by 75 IU
- On stimulation day 3 if E2 < 75, increase by 75 IU
- On stimulation day 5 if E2 > 500, decrease by 75 IU
- On stimulation day 5 if E2 < 150, increase by 75 IU

clinical outcomes in oocyte donors with a significantly lower basal antral follicle count (BAFC). In donors with a high BAFC (>30), this management strategy also minimizes the risk of OHSS (1/249) (16). Following day 5, all monitoring is done with ultrasounds only unless the cycle does not appear to be progressing normally, that is, poor follicle number or growth pattern.

Recipients

Downregulation of Recipient

Prior to the uterine preparation treatment, downregulation of the cycle is usually performed due to studies that have clearly indicated that adequate downregulation of the menstrual cycle beforehand is beneficial. Borini et al. (17) studied the effect of long-term downregulation on pregnancy and implantation rates in 122 cyclic patients who received donor oocytes. Recipients who were either menopausal or cyclic but had long-term downregulation had significantly higher pregnancy and implantation rates. Apart from the improved pregnancy and implantation rates after long-term downregulation, these data not only demonstrate an important role of the endometrium in implantation but also suggest that a period of amenorrhea improves the pregnancy rate.

In cyclic patients (patients with natural menstrual cycles), suppression of the cycle is accomplished with a GnRH-agonist analogue (Lupron®). Lupron has the added advantage that it can be used for several months at a time without causing any permanent changes to the reproductive system or detrimental effect on the success of the cycle. This ensures a degree of flexibility that allows egg donation to function successfully.

Estrogen Replacement for Recipients

Lutjen et al. (18) first reported egg donation to a recipient with premature ovarian failure in 1984. They used a steroid replacement regimen for the recipient consisting of estrogen valerate (Progynova®; Schering, Sydney, Australia) and progesterone suppositories (Utrogestan®; Piette, Brussels, Belgium). Since then, many different regimens of estrogen and progesterone replacement have been tried successfully, differing in both the method of administration and timing.

There are many reports dealing with the recommended type and dosage of estrogen and progesterone supplementation in artificial endometrial preparation before the transfer of embryos. We know from oocyte donation programs that maximum flexibility is necessary to synchronize the recipient until oocytes are available. The aim is an open so-called window of implantation with a highly receptive-appearing endometrium at the time of embryo transfer. This period lasts a maximum of 48 hours. At the end of endometrial preparation, there should be an overlapping between the "window of transfer," during which a transfer is planned, and the "window of implantation."

Many studies have examined the effects of different estrogen replacement regimens. Most have shown that the length of estrogen administration could be varied and delayed. In fact, successful implantation was observed in an extreme situation even after 100 days of unopposed estradiol valerate administration (19). Ovulatory patients in this study received a GnRH analogue simultaneously. Breakthrough bleeding increasingly appeared according to the duration of estrogen replacement. These clinical observations provide evidence that the concept of "prolonged follicular phase" estrogen replacement for ovum donation can be maintained, at least for as long as 15 weeks. Because of the high incidence of breakthrough bleeding after nine weeks (>44%), the authors recommended stopping estrogen replacement after this time. Yaron et al. (20) extended uterine preparation with estradiol for as long as five weeks without significantly decreased pregnancy rates.

It was suggested that shorter and lower dosage protocols of estradiol priming of the endometrium could result in higher abortion rates. This indicates an optimal endometrial proliferation that is necessary to enable optimal development of progesterone receptors and subsequent transformation into an endometrium receptive to the transferred embryo (21). Neither endometrial thickness nor serum estradiol was able to predict optimal receptivity and therefore outcome in oocyte donation.

At Boston IVF, we continue estrogen replacement (both oral and transdermal) until 10 weeks' estimated gestational age (EGA).

Table 9.8 Administration of Medications

Class of medication	Typical form
Oral contraceptives	Oral tablet
Luveris®	Subcutaneous injection
Cetrotide®/Ganirelix	Subcutaneous injection
Lupron®	Subcutaneous injection
Estrogen	Oral tablet; skin patch
Progesterone	Vaginal gel, vaginal suppository, or intramuscular injection

Progesterone Replacement for Recipients

Much controversy surrounds the issue of progesterone replacement in DE IVF cycles. Unfortunately, prospective studies comparing different types and durations of progesterone supplementation before transfer of DE IVF embryos with regard to treatment outcome have not yet been performed. With regard to timing of progesterone, several retrospective studies have shed light on the implantation window. In one study, four to five days of progesterone administration were optimal for embryo transfer comparing results after transfers between day 2 and day 7 of progesterone administration. Rosenwaks (22) reported best results after transfers on day 3 to 5 of progesterone supplementation.

Prapas et al. (23) performed an interesting retrospective study on the association between the window of embryo transfer and the duration of progesterone therapy. They transferred day 2 embryos (4–6 cells) after two, three, four, five, and six days following initiation of endometrial exposure to progesterone. The results indicate that the window of implantation depends on the duration of progesterone treatment. It begins ~48 hours after starting progesterone administration and lasts for ~four days. Highest pregnancy rates were achieved after five days (48.3%), with lower rates after four days (40%), six days (20.4%), and three days (12%). No pregnancies were observed after two days of progesterone administration.

Progesterone is also a critical factor in the late follicular phase of fresh IVF cycles. There is much debate on the question of whether a subtle, late follicular phase, pre-hCG rise of progesterone above a certain threshold (1.0 ng/mL) has an impact on the outcome of treatment in IVF cycles. Considering all information, there seems to be no effect on oocyte and embryo quality and therefore no reason to cancel DE IVF cycles when progesterone measurements are over that threshold.

We use both vaginal and intramuscular progesterone replacement regimens and have not seen a difference in success rates. The medications and forms of administration are listed in Table 9.8. As with the estrogen replacement, we continue progesterone replacement until 10 weeks' EGA.

Recipient Monitoring

In most cases, recipients are monitored only once with an ultrasound to measure the endometrial thickness. This typically occurs on day 5 to 7 of the donor's stimulation cycle. This allows us to adjust the medications in the event that the lining is not adequate (≥7 mm) (24).

GESTATIONAL CARRIER IVF

In 1985, Utian et al. (25) described the first successful pregnancy using a gestational carrier. The patient had undergone a hysterectomy. She had her eggs removed and then fertilized with her husband's sperm. The embryos were then transferred into the gestational carrier. There are two groups of patients that are candidates for gestational carrier IVF (GC-IVF): women without a functioning uterus or those whose pregnancy would severely exacerbate a medical condition. It is important to note that IVF with a gestational carrier differs from traditional surrogacy. In a traditional surrogacy arrangement, the surrogate mother provides the oocyte *and* the uterus to foster a pregnancy. With a GC-IVF cycle, the gestational carrier is not the genetic mother because she does not provide the oocyte. At Boston IVF, we do not participate in traditional surrogacy treatment.

Prescreening and Counseling

At our center, the minimum age of gestational carriers is 21 years, with an upper limit of 40 at the initiation of the IVF cycle. All gestational carriers must have carried at least one child and preferably have completed their families. As with egg donor and recipients, both genetic mothers (intended parents or IPs) and gestational carriers undergo prenatal screening as recommended by the guidelines of the ASRM. Before ovarian stimulation, issues discussed with the IPs, the gestational carrier, and her partner, include selective reduction for multiple gestations in excess of twins, chorionic villus sampling, amniocentesis, risks of the procedure, and mode of delivery. All of the IPs, the gestational carriers, and their partners undergo psychological and legal counseling, including appropriate legal contracts. Unlike DE IVF, there are no agencies and therefore legal contracts must be done with an attorney specializing in reproductive law. It is important that the IPs and the gestational carrier have separate representation.

Cycle Synchronization and Ovulation Induction

Cycle synchronization between the IPs and the gestational carrier is achieved after downregulation with leuprolide acetate. The stimulation protocols and ovulation induction protocols are identical to those previously described for DE IVF. Estrogen replacement for the carrier (both oral and transdermal) and progesterone replacement are continued until 10 weeks' EGA.

FDA Regulations

Both the IPs are regarded as "gamete donors" according to FDA regulations (7). The intended mother must therefore be screened for the same tests as an oocyte donor up to 30 days prior to the egg retrieval (Table 9.2), and the intended father must be screened for the required tests (Table 9.3) within seven days before or after the egg retrieval.

EMBRYO DONATION

In the current practice of ART, more embryos are created than can be transferred during the cycle. Embryos that meet criteria for cryopreservation are stored for future use by the patients. When the genetic parents decide that their family is complete and embryos are still available, they are faced with a dilemma: donating their embryos to research, thawing them and letting them die, or donating them to a couple who is unable to conceive. A survey sent to all 430 ART facilities in the United States in 2002 estimated that a total of 396,526 embryos had been placed in storage in the United States (26). In 2011, this number is estimated to have increased to well over 500,000 embryos.

In 2009, the ethics committee of the ASRM issued a report strongly objecting to the term embryo "adoption" as inaccurate and misleading (27). Their point is that donating an embryo to another person is a medical procedure, subject to the rules and regulations for medical procedures, not subject to the legal and social work regulations associated with adoption of an actual human being. On the other hand, in spite of ASRM's insistence that donation of embryos is strictly a medical procedure, there are embryo donation programs on the Internet that will arrange "open" embryo adoptions, allowing the donor and recipient to actually share the future child as in traditional open adoptions of existing children. Some embryo adoption agencies will allow the donor to choose the recipient of their embryos. As with donor oocyte, donor sperm, and gestational carrier procedures, in the United States, the FDA oversees the process through comprehensive regulations that apply to all donated human tissues, reproductive and nonreproductive alike.

In 2008, the ASRM issued guidelines for ART practices that offer embryo donation (28). The guidelines stated that the practice should be knowledgeable in the storage, thawing, and transfer of frozen embryos, the practice may charge a professional fee to the potential recipients for embryo thawing, the embryo transfer procedure, cycle coordination and documentation, and infectious disease screening and testing of both recipients and donors. However, the selling of embryos per se is ethically unacceptable. Embryos should be quarantined for a minimum of six months before the potential donors are screened and tested or retested, with documentation of negative results. Lastly, physicians and employees of an

infertility practice should be excluded from participating in embryo donation as either donors or recipients within that practice.

For embryos derived from gametes obtained from an anonymous donor or donors, the donor or donors must have met all FDA screening and testing requirements and must have been determined eligible for anonymous donation. If donor sperm were used, the sperm donor must have met all current FDA requirements for donation, the sperm sample used to fertilize the oocytes must have met the minimum six-month quarantine requirement for donor sperm, and the female partner must have met all screening and testing requirements for oocyte donors within the 30 days preceding oocyte retrieval. If donor oocytes were used, the oocyte donor must have met all current FDA requirements for donation within the 30 days preceding the oocyte retrieval, and the male partner must have met all screening and testing requirements, to include the minimum six-month quarantine for donor sperm. Embryos derived from the gametes of a sexually intimate couple and created for use by that couple are exempt from the requirements for donor screening and testing before creation of the embryos.

Per the ASRM guidelines, the decision to proceed with embryo donation is complex, and patients may benefit from psychological counseling to aid in this decision. Psychological consultation with a qualified mental health professional should be offered to all couples participating in the donor-embryo process. The physician should require psychological consultation for couples in whom there appear to be factors that warrant further evaluation (28).

SPERM DONATION

Sperm donation is the most common type of gamete donation. The guidelines for sperm donation have been published by the ASRM (27). There are several indications for sperm donation including male factor infertility, when the male partner is a carrier of a genetic condition or has a transmissible disease that cannot be eradicated and for the woman who does not have a male partner. Prior to the outbreak of HIV it was common that fresh donor sperm samples were used but now exclusively frozen sperm samples are obtained from licensed sperm banks. The frozen sperm samples are quarantined for a period of six months and only released after the donor has tested negative for syphilis, hepatitis, and HIV. More commonly the sperm donation is done anonymously but on occasion the choice is a known donor. For a couple, the male partner may desire to use a relative such as a brother or less commonly his father for the sperm donor since this will allow him to have a genetic tie to the offspring. A single woman may choose an identified sperm donor as well. It is standard that any couple or woman pursuing sperm donation meet with a social worker for counseling. In cases of known sperm donation, all parties will meet with the social worker over several sessions before moving forward. In cases of known sperm donation, it is also of extreme importance that legal counseling be obtained to specify who controls the sperm samples, the parental rights and obligations of the recipient woman or couple, and the lack of obligations of the sperm donor. This legal counseling should result in the development of a contract that protects all parties involved.

Evaluation

1. hysterosalpingogram (HSG)
2. Cycle day 3 FSH, E2, thyroid-stimulating hormone (TSH)
3. Prenatal blood work and indicated genetic testing based on ancestral background
4. Cytomegalovirus (CMV) IgG and IgM titers—if the woman is found to be CMV negative, then she should choose a CMV-negative donor. CMV is a herpes virus and there is concern that a CMV-positive donor may excrete active virus in the semen
5. Cervical cultures
6. Male partner (of recipient couple) should be screened for rapid plasma regain (RPR), hepatitis B antigen, hepatitis C antibody, HIV
7. Consultation with social worker

REFERENCES

1. Bloom DE, Trussell J. What are the determinants of delayed childbearing and permanent childlessness in the United States? Demography 1984; 21(4):591–611.
2. CDC. CDC 2009 Assisted Reproductive Technology (ART) Report, 2009.
3. 2008 Assisted Reproductive Technology Report. Available at: http://www.cdc.gov/art/. Accessed 20 February, 2011.
4. Joseph KS, Allen AC, Dodds L, et al. The perinatal effects of delayed childbearing. Obstet Gynecol 2005; 105(6):1410–1418.
5. Benagiano G. Pregnancy after the menopause: a challenge to nature? Hum Reprod 1993; 8(9):1344–1345.
6. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005; 352(11):1138–1145.
7. Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products. Final Rule. Fed Regist 2004; 69(101):29785–29834.
8. Human cells, tissues, and cellular and tissue-based products; donor screening and testing, and related labeling. Interim final rule; opportunity for public comment. Fed Regist 2005; 70(100):29949–29952.
9. Shulman A, Frenkel Y, Dor J, et al. The best donor. Hum Reprod 1999; 14(10):2493–2496.
10. Cohen MA, Lindheim SR, Sauer MV. Donor age is paramount to success in oocyte donation. Hum Reprod. 1999; 14(11):2755–2758.
11. Financial incentives in recruitment of oocyte donors. Fertil Steril 2004; 82(suppl 1):S240–S244.
12. Damario MA, Barmat L, Liu HC, et al. Dual suppression with oral contraceptives and gonadotrophin-releasing hormone agonists improves in-vitro fertilization outcome in high responder patients. Hum Reprod 1997; 12(11):2359–2365.
13. Barmat LI, Chantilis SJ, Hurst BS, et al. A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. Fertil Steril 2005; 83(2):321–330.
14. Morris RS, Paulson RJ, Sauer MV, et al. Predictive value of serum oestradiol concentrations and oocyte number in severe ovarian hyperstimulation syndrome. Hum Reprod 1995; 10(4):811–814.
15. Berger BM, Ezcurra D, Alper MM. A standardized protocol with minimal monitoring for controlled ovarian stimulation of egg donors results in improved pregnancy rates. Fertil Steril 2004; 82:S121.
16. Berger BM, Ezcurra D. Treatment modification based on basal antral follicle count maintains high pregnancy rates while preventing OHSS in egg donor IVF. Fertil Steril 2009; 92:S3.
17. Borini A, Violini F, Bianchi L, et al. Improvement of pregnancy and implantation rates in cyclic women undergoing oocyte donation after long-term down-regulation. Hum Reprod 1995; 10(11):3018–3021.
18. Lutjen P, Trounson A, Leeton J, et al. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 1984; 307(5947):174–175.
19. Remohi J, Gutierrez A, Cano F, et al. Long oestradiol replacement in an oocyte donation programme. Hum Reprod 1995; 10(6):1387–1391.
20. Yaron Y, Amit A, Mani A, et al. Uterine preparation with estrogen for oocyte donation: assessing the effect of treatment duration on pregnancy rates. Fertil Steril 1995; 63(6):1284–1286.
21. Navot D, Scott RT, Droesch K, et al. The window of embryo transfer and the efficiency of human conception in vitro. Fertil Steril 1991; 55(1):114–118.
22. Rosenwaks Z. Donor eggs: their application in modern reproductive technologies. Fertil Steril 1987; 47(6):895–909.
23. Prapas Y, Prapas N, Jones EE, et al. The window for embryo transfer in oocyte donation cycles depends on the duration of progesterone therapy. Hum Reprod 1998; 13(3):720–723.
24. Zenke U, Chetkowski RJ. Transfer and uterine factors are the major recipient-related determinants of success with donor eggs. Fertil Steril 2004; 82(4):850–856.
25. Utian WH, Sheean L, Goldfarb JM, et al. Successful pregnancy after in vitro fertilization and embryo transfer from an infertile woman to a surrogate. N Engl J Med. 1985; 313(21):1351–1352.
26. Hoffman DI, Zellman GL, Fair CC, et al. Cryopreserved embryos in the United States and their availability for research. Fertil Steril 2003; 79(5):1063–1069.
27. American Society for Reproductive Medicine: defining embryo donation. Fertil Steril 2009; 92:1818–1819.
28. 2008 Guidelines for gamete and embryo donation: a Practice Committee report. Fertil Steril 2008; 90: S30–S44.

10 Overview of male infertility

Stephen A Lazarou

INTRODUCTION

Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is responsible in about 20% of infertile couples and contributory in another 30% to 40% (1). Male infertility is generally determined by the finding of an abnormal semen analysis, although other factors may play a role in the setting of a normal semen analysis.

Male infertility can be due to a variety of conditions. Some of these conditions are potentially reversible, such as obstruction of the vas deferens and hormonal imbalances. Other conditions are not reversible, such as bilateral testicular atrophy secondary to a viral infection.

Treatment of various conditions may improve male infertility and allow for conception through intercourse. Even men who have absent sperm on their semen analyses (azoospermia) may have sperm production by their testicles. Detection of conditions for which there are no treatments spares couples the distress of attempting therapies that are not effective. Identifying certain genetic causes of male infertility allows couples to be informed about the potential to transmit genetic conditions that may affect the health of offspring. Therefore, a comprehensive evaluation of the male partner allows the couple to better understand the basis of their infertility and to obtain genetic counseling where necessary. Male infertility may be the presenting manifestation of an underlying life-threatening condition, such as testicular or pituitary tumors (2).

If corrective treatment is not available, assisted reproductive techniques (ART) such as testicular or epididymal sperm retrieval in combination with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) may be utilized. Other options for couples include donor insemination or adoption.

WHEN TO EVALUATE THE MALE

A couple attempting to conceive should have an evaluation for infertility if pregnancy does not occur within one year of regular unprotected intercourse. An evaluation should be done before one year if male infertility risk factors, such as a history of bilateral cryptorchidism (undescended testes) or chemotherapy, are known to be present. Other reasons may include female infertility risk factors, including advanced female age (over the age of 35) or a couple that questions the male partner's fertility potential. While a man may have a history of being previously involved in a pregnancy, this does not exclude the possibility that he has acquired a new factor preventing normal fertility (secondary infertility). Men with secondary infertility should be evaluated in the same comprehensive way as men who have never initiated a pregnancy.

EVALUATION OF THE INFERTILE MALE

The evaluation of the infertile male should be performed by a urologist and include a complete reproductive and medical history, physical examination, and at least two semen analyses ideally separated by at least a week. The reproductive and medical history should include coital frequency and timing, duration of infertility and prior fertility, childhood illnesses and developmental history, systemic medical illnesses (e.g., diabetes mellitus and upper respiratory diseases) and prior surgeries (e.g., hernia repair), sexual history including sexually transmitted infections, and exposure to toxins from heat, chemicals, and radiation, including smoking and family reproductive history, review of systems, and allergies.

Physical Examination

A general physical examination is an essential part of the evaluation. In addition to the general physical examination, particular attention is given to the genitalia including (*i*) examination of the penis including the location of the urethral meatus; (*ii*) palpation of the testes and measurement of their size; (*iii*) presence and consistency of both the vasa and epididymides;

Table 10.1 Normal Reference Values for Semen Analysis

Ejaculatory volume	2.0–5.0 mL
pH	>7.2
Sperm concentration	>20 million/mL
Total sperm number	>40 million/ejaculate
% Motile	>50%
Forward progression	>2 (scale 0–4)
Normal morphology	>50% normal[a]
	>30% normal[b]
	>14% normal[c]

[a]World Health Organization, 1987 (7).
[b]World Health Organization, 1992 (8).
[c]Kruger (Tygerberg) Strict Criteria; World Health Organization, 1999 (4).

Table 10.2 Fertile, Indeterminate, and Subfertile Ranges for Sperm Measurements and Corresponding Odds Ratios for Infertility

	Semen measurement		
Variable	Concentration ($\times 10^6$/mL)	Motility (%)	Morphology (% nml)
Fertile range	>48.0	>63	>12
Indeterminate range	13.5–48.0	32–63	9–12
Univariate odds ratio for infertility (95% CI)	1.5 (1.2–1.8)	1.7 (1.5–2.2)	1.8 (1.4–2.4)
Subfertile range	<13.5	<32	<9
Univariate odds ratio for infertility (95% CI)	5.3 (3.3–8.3)	5.6 (3.5–8.3)	3.8 (3.0–5.0)

Source: From Ref. 3.

(*iv*) presence of a varicocele; (*v*) secondary sex characteristics including body habitus, hair distribution, and breast development; and (*vi*) digital rectal exam.

On the basis of the results of the full evaluation, the urologist may recommend other procedures and tests to determine the cause of a patient's infertility. These tests may include additional semen analyses, hormone evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests of semen, and genetic screening.

Semen Analysis

A semen analysis is the principal laboratory evaluation of the infertile male and helps to define the severity of the male factor. An abstinence period of two to three days is necessary before semen can be collected by masturbation or by intercourse using special semen collection condoms that do not contain substances detrimental to sperm (i.e., lubricants). The specimen may be collected at home or at the laboratory. The specimen should be kept at room, or ideally body, temperature during transport and examined within one hour of collection.

The semen analysis provides information on semen volume as well as sperm concentration, motility, and morphology (Table 10.1). Values that fall outside these ranges indicate the need for consideration of additional clinical/laboratory evaluation of the patient. It is important to note that reference values for semen parameters are not the same as the minimum values needed for conception, and that men with semen variables outside the reference ranges may be fertile. In a study comparing 765 infertile couples with 696 fertile couples (Table 10.2), the threshold values for sperm concentration, motility, and morphology were used to classify men as subfertile, of indeterminate fertility, or fertile. None of the measures, however, were entirely diagnostic of infertility. In fact, patients with values within the reference range may still be subfertile (3).

Absent sperm in the ejaculate, or azoospermia, is not diagnosed unless the specimen is centrifuged and the pellet is examined. The evaluation of sperm morphology (shape) has changed considerably over time. Sperm morphology assessment by strict (Kruger) criteria has been used to identify couples who have a poor chance of fertilization with standard IVF (4,5) or a better chance of fertilization with ICSI (6). The WHO criteria of 1987 and 1992 (7,8) that

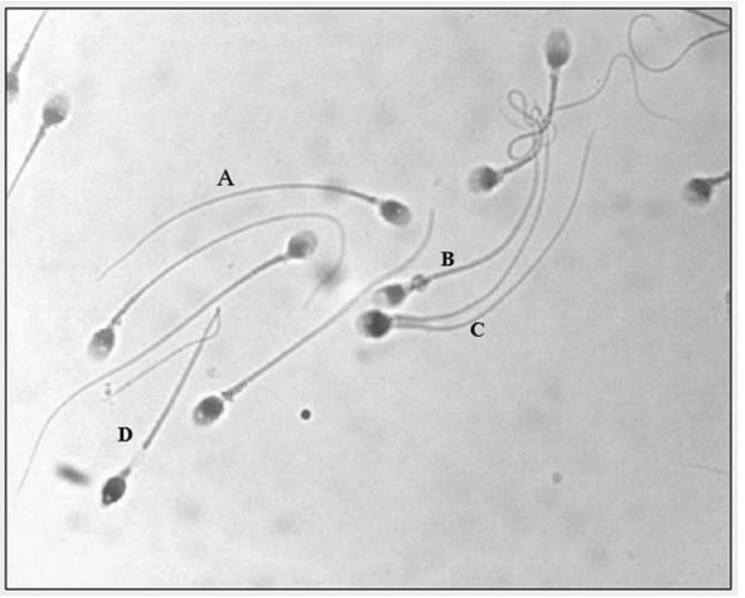

Figure 10.1 Examples of varied sperm morphology: A, normal; B, mid-piece defect; C, tail defect; D, tapered head.

classify more sperm in the normal category are also widely used in the routine semen evaluation. True reference ranges have not been established for semen parameters (Fig.10.1).

Endocrine Evaluation

Hormonal abnormalities of the hypothalamic-pituitary testicular axis are well-known causes of male infertility. Endocrine laboratory work should be obtained if there is an abnormal semen analysis, impaired sexual function, or other clinical findings suggestive of a specific endocrinopathy. The initial hormonal evaluation should consist of measurements of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin. The relationship of testosterone, LH, FSH, and prolactin helps to identify various clinical conditions, such as primary testicular failure or pituitary dysfunction. A normal serum FSH level does not guarantee the presence of intact spermatogenesis. However, an elevated FSH level even in the upper range of "normal" is indicative of an abnormality in spermatogenesis.

Post-Ejaculatory Urinalysis

Low-volume or absent ejaculate suggests retrograde ejaculation (semen going back into the bladder instead of out the urethra), lack of emission, ejaculatory duct obstruction, hypogonadism (low testosterone), or congenital bilateral absence of the vas deferens (CBAVD). Other explanations of low-volume ejaculate are incomplete collection and short periods (<2 days) of abstinence. Retrograde ejaculation can occur in men who have diabetes and those with testicular cancer who have undergone a lymph node dissection that can disrupt the sympathetic nerves. To diagnose possible retrograde ejaculation, a post-ejaculatory urinalysis (analysis of urine sample after ejaculation) should be performed for any man whose ejaculatory volume is low and who has not been diagnosed with hypogonadism or CBAVD.

The post-ejaculatory urinalysis is performed by centrifuging the specimen and microscopically inspecting the pellet. The presence of any sperm in a post-ejaculatory urinalysis of a patient with azoospermia is suggestive of retrograde ejaculation. Significant numbers of sperm must be found in the urine of patients with low ejaculate volume oligospermia in order to suggest the diagnosis of retrograde ejaculation.

Ultrasonography

Scrotal Ultrasonography

Most scrotal abnormalities are visible and palpable on physical examination. These include varicoceles (dilated veins in the scrotum; Fig. 10.2), spermatoceles (epididymal cysts; Fig. 10.3),

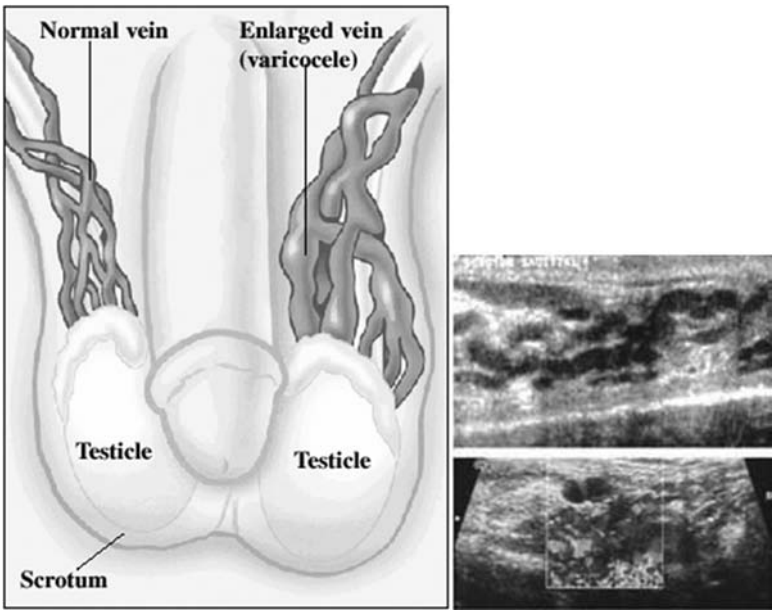

Figure 10.2 Left-sided varicocele with dilated veins identified by scrotal ultrasonography.

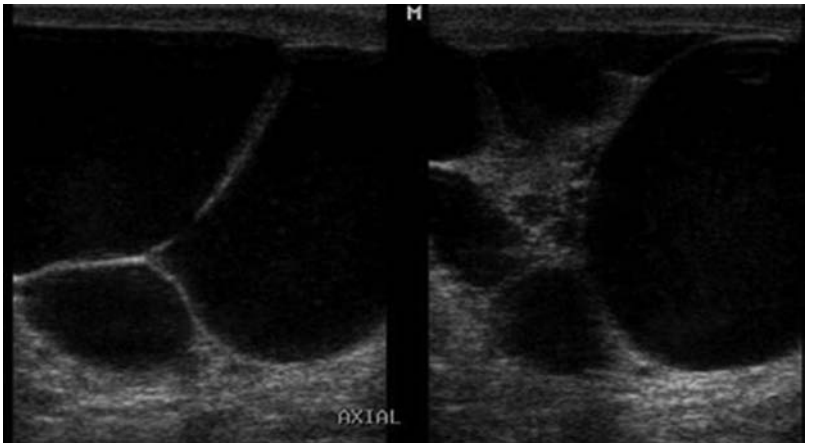

Figure 10.3 Ultrasonographic images of epididymal cysts (spermatocele).

absence of the vas deferens, epididymal induration, and testicular masses. Scrotal ultrasonography may identify nonpalpable varicoceles. Scrotal ultrasonography may be useful to clarify ambiguous findings on examination, such as may occur in patients with testes that are in the upper scrotum, small scrotal sacs, or other anatomy that makes physical examination difficult.

Transrectal Ultrasonography

The finding of dilated seminal vesicles, dilated ejaculatory ducts, and/or midline prostatic cystic structures on transrectal ultrasonography (TRUS) is suggestive of complete or partial ejaculatory duct obstruction (9). Normal seminal vesicles are less than 2 cm in anteroposterior diameter (10). Patients with complete ejaculatory duct obstruction produce low-volume, fructose-negative, acidic, azoospermic ejaculates and may have dilated seminal vesicles identified by ultrasound (Fig. 10.4). Patients with CBAVD may also have these findings because they often have absent or atrophic seminal vesicles. Patients with partial ejaculatory

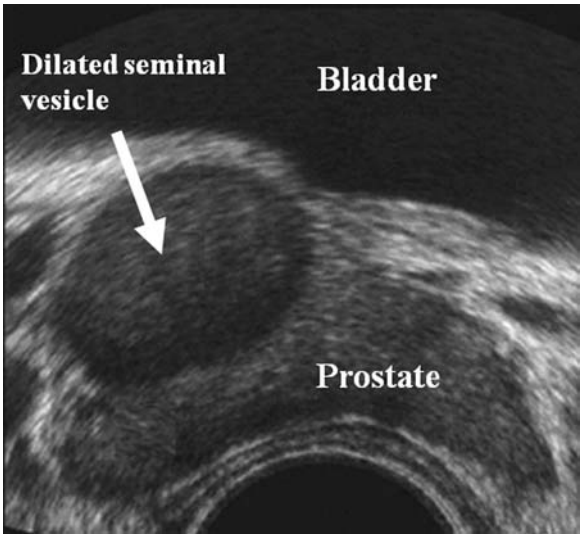

Figure 10.4 Rectal ultrasound examination confirming a dilated seminal vesicle as a result of obstruction.

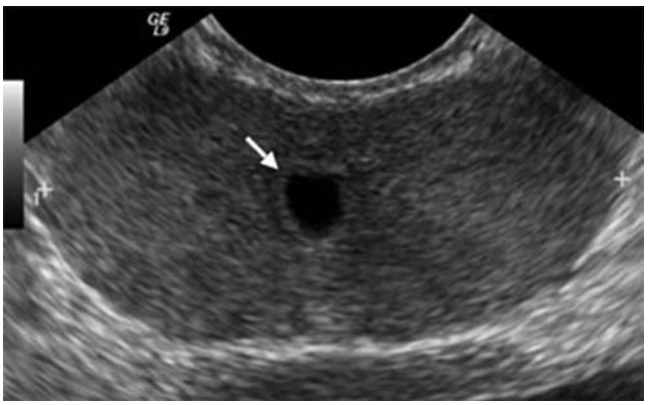

Figure 10.5 Ejaculatory duct cyst associated with an obstruction.

duct obstruction often present with low volume, diminished sperm concentration, and/or poor motility. Cysts at the ejaculatory ducts may be identified by ultrasonography and are occasionally amenable to transurethral resection or "unroofing" (Fig. 10.5).

SPECIALIZED CLINICAL TESTS ON SEMEN AND SPERM

In some cases, semen analyses fail to accurately predict a man's fertility. Specialized clinical tests should be reserved only for those cases in which identification of the cause of male infertility will direct treatment.

Strict Sperm Morphology

The clinical implications of poor morphology are controversial. Initial studies evaluating the utility of strict sperm morphology in predicting fertilization rates during IVF used a score of greater than 14% for normal. However, subsequent studies report fertilization rates being lowest for patients with morphology scores of less than 4%. Pregnancy rates have also been reported to be suboptimal with lower scores but some recent studies have reported no relationship of morphology to IVF results (10,11). The relationship between morphology scores and pregnancy rates with intrauterine insemination (IUI) and intercourse have been examined (12–16). However, there is no consensus on the implications of poor morphology

scores. Furthermore, the interpretation of sperm morphology varies from lab to lab. However, certain rare morphological abnormalities, such as sperm without acrosomes, are highly predictive of failure to fertilize eggs. Yet in most cases, fertilization and pregnancy are possible even with very low morphology scores. Although most physicians utilize strict morphology in practice, most studies have not addressed the significance of isolated low morphology in patients with otherwise normal semen parameters.

DNA Integrity

DNA integrity testing refers to a variety of assays utilized to evaluate the degree of sperm DNA fragmentation. Assessment of sperm DNA integrity has been evaluated for correlation with the ability to conceive by intercourse, IUI, IVF, and IVF using ICSI. Studies demonstrate a statistically significant lower pregnancy rate in those patients with impaired sperm DNA integrity. Nonetheless, many couples with impaired sperm DNA integrity conceive by intercourse (17–19). The tests are inadequate as screening tests for pregnancy by intercourse. One large study has suggested that abnormal DNA integrity in the sample used for IUI was predictive of pregnancy rates (20). Most studies have examined the predictive value of sperm DNA integrity testing in routine IVF and IVF using ICSI. Meta-analysis of published studies has found a small, statistically significant, predictive effect of DNA integrity results on pregnancy rates for IVF with or without ICSI (21–23). Limited data suggest DNA integrity testing may be of value in identifying those at risk for recurrent pregnancy loss (24). However, there is insufficient evidence to warrant routine testing.

Reactive Oxygen Species

Elevated reactive oxygen species (ROS) have been implicated as a cause of male infertility. Both sperm and white blood cells in the semen can produce ROS. ROS can interfere with sperm function by peroxidation of sperm lipid membranes and creation of toxic fatty acid peroxides. Controversy exists regarding the best method of testing for ROS and whether therapies are effective at reducing seminal ROS and improving fecundity. Routine clinical testing and treatment of ROS are not indicated at this time.

Quantitation of Leukocytes in Semen

An elevated number of leukocytes (white blood cells) in the semen has been associated with decreased sperm function and motility. Under microscopy, both leukocytes and immature germ cells appear similar and are properly termed "round cells." The lab must make sure that the two types of cells are differentiated to differentiate between a possible infection and immature sperm. A variety of assays are available to differentiate leukocytes from immature germ cells (25). Men with true pyospermia (>1 million leukocytes/mL) should be evaluated for a genital tract infection or inflammation. A semen culture may also be of value to determine the presence of microorganisms.

Tests for Antisperm Antibodies

Pregnancy rates may be reduced by antisperm antibodies (ASA) in the semen (26). Risk factors for ASA include ductal obstruction, prior genital infection, testicular trauma, and prior vasectomy and reversal. ASA testing may be considered when there is isolated poor motility with normal sperm concentration, sperm agglutination, or an abnormal postcoital test. Some physicians recommend ASA testing for couples with unexplained infertility. ASA testing is not needed if sperm are to be used for ICSI.

Sperm Viability Tests

Sperm viability can be assessed by mixing fresh semen with a dye such as eosin or trypan blue, or by the use of hypo-osmotic swelling (HOS) test. These assays determine whether nonmotile sperm are viable by identifying which sperm have intact cell membranes. Nonmotile but viable sperm, as determined by the HOS test, may be used successfully for ICSI. In the HOS test, sperm are placed into two different mediums (first in a solution called polyvinylpyrrolidone (PVP), and then in the actual HOS medium itself consisting of sperm wash media and water) and then are left to sit for 30 seconds. At this point, the sperm are observed for the presence of

curled or kinked tails, which indicate viability. The viable sperm can then be extracted and used for ICSI.

Tests of Sperm–Cervical Mucus Interaction

The postcoital test is the microscopic examination of the cervical mucus performed before expected ovulation and within hours after intercourse to identify the presence of motile sperm in the mucus. It is used to identify cervical factors that contribute to infertility. Examination may reveal gross evidence of cervical inflammation that can be treated. Although its value has been seriously questioned (27), some physicians still consider it a useful diagnostic test because it may help to identify ineffective coital technique or a cervical issue (27).

Zona-Free Hamster Oocyte Penetration Test

Removal of the zona pellucida from hamster oocytes allows human sperm to fuse with hamster ova. This test is often termed a sperm penetration assay (SPA). For penetration to occur, sperm must undergo a series of reactions to integrate into the egg (capacitation, the acrosome reaction, fusion with the oolemma, and incorporation into the ooplasm). SPA has been used clinically, and the value of the test results depends on the experience of the laboratory performing the test (28). Although this test was used in the past, it is very rarely used presently.

Computer-Aided Sperm Analysis

Computer-aided sperm analysis (CASA) requires sophisticated instruments for quantitative assessment of sperm from a microscopic image or from videotape. CASA is used to measure sperm numbers, motility, and morphology. CASA is useful for assessing sperm motility and motion, such as velocity or speed and head movement, which are important factors in determining sperm fertility potential. While the use of CASA would provide better standardization of the semen analysis, the cost has prevented most centers from utilizing this technology.

Genetic Screening

Genetic abnormalities may cause infertility by affecting sperm production and/or transport. The three most common genetic factors known to be related to male infertility are cystic fibrosis gene mutations associated with CBAVD, chromosomal abnormalities resulting in impaired testicular function, and Y-chromosome microdeletions associated with impaired spermatogenesis. Azoospermia and severe oligospermia (sperm concentration <5 million/mL) are more often associated with genetic abnormalities. Men with nonobstructive azoospermia and severe oligospermia should be informed that they might have chromosomal abnormalities or Y-chromosome microdeletions. Genetic counseling should be offered whenever a genetic abnormality is found.

Cystic Fibrosis Gene Mutations

The most common cause of CBAVD is a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Almost all males with clinical cystic fibrosis have CBAVD. Approximately 70% of men with CBAVD and no clinical evidence of cystic fibrosis have an identifiable abnormality of CFTR gene (29,30). Since normal vasa are palpable within the scrotum, the diagnosis of vasal absence (agenesis), either bilateral or unilateral, is established by physical examination. Imaging studies and surgery are not necessary to confirm the diagnosis but may be useful for diagnosing abnormalities associated with vasal agenesis. Most patients with vasal agenesis also have malformed or absent seminal vesicles. Since the majority of semen is derived from the seminal vesicles, almost all patients with CBAVD have low semen volume. In the azoospermic patient who has unilateral vasal agenesis, radiologic imaging with TRUS may be useful to evaluate the ampullary portion of the contralateral vas deferens and the seminal vesicles, because unilateral vasal agenesis can be associated with contralateral segmental abnormality of the vas deferens or seminal vesicle, resulting in obstructive azoospermia (31).

It is recommended that both partners undergo genetic counseling and testing of the CFTR gene to rule out abnormalities. Failure to identify a CFTR abnormality in a man with CBAVD, however, does not absolutely rule out the presence of a mutation, since many are undetectable

by routine testing methods. It is important to test the partner for CFTR gene abnormalities prior to performing a treatment that utilizes his sperm because of the risk that she may be a carrier.

Genetic testing of the patient with CBAVD is important due to future health effects of CFTR mutations as well as counseling siblings about their risk of being carriers of CFTR mutations (32,33). There is a strong association between unilateral vasal agenesis and kidney abnormalities due to their common embryological origin. Interestingly, the association of renal anomalies and CBAVD is much weaker with a prevalence of only 11%. However, for those patients who have CBAVD and CFTR mutations, the prevalence of renal anomalies is extremely rare (34). Therefore, imaging of the kidneys with either ultrasound or CT scan is more likely to detect abnormalities in men with unilateral vasal agenesis or men with CBAVD who do not have mutations in CFTR.

Karyotype

A karyotype analyzes all chromosomes for the gain or loss of entire chromosomes as well as structural defects, including chromosome rearrangements (translocations), duplications, deletions, and inversions. Chromosomal abnormalities account for about 6% of all male infertility and the prevalence increases with poorer semen parameters (i.e., severe oligospermia and nonobstructive azoospermia). Paternal transmission of chromosome defects can result in pregnancy loss, birth defects, male infertility, and other syndromes. Karyotypes should be ordered in men with severe oligospermia (sperm concentrations <5 million/mL) and azoospermia.

Y-Chromosome Microdeletions

Approximately 13% of men with nonobstructive azoospermia or severe oligospermia have an underlying Y-chromosome microdeletion (deletion in the Y chromosome) (35). Y-chromosome microdeletions responsible for infertility [azoospermic factor (AZF) regions a, b, or c] are detected using sequence tagged sites (STS) and polymerase chain reaction (PCR) analysis. Successful testicular sperm extraction has not been reported in infertile men with either an AZFa or AZFb deletion but the total number of reports is limited. In contrast, up to 80% of men with AZFc deletions have sperm that can be retrieved for ICSI. The couple must be counseled on the transmission of the gene to all male offspring (36,37).

TREATMENTS FOR MALE INFERTILITY

There are several causes of infertility for which there is no treatment. For instance, there are no current treatments to stimulate sperm production when the seminiferous tubules have been severely damaged. Examples include Klinefelter syndrome and Y-chromosome microdeletions.

In contrast, some azoospermic conditions, such as in those with obstruction, may have sperm that can be extracted from the seminiferous tubules of the testes. If mature sperm are obtained they can be cryopreserved or used immediately to fertilize oocytes through IVF. Even in cases with primary testicular failure, such as Klinefelter syndrome, sperm retrieval techniques can be employed along with ICSI (38). There are important genetic ramifications for these procedures (39).

Specific endocrine treatment is available for men whose infertility results from hypogonadotropic hypogonadism, that is, from a pituitary/hypothalamic abnormality in which the pituitary gland does not properly release gonadotropic hormones that stimulate the testes. If hypogonadotropic hypogonadism results from hyperprolactinemia (elevated prolactin levels), the hypogonadism can often be corrected and fertility restored by lowering the serum prolactin concentration. If the hyperprolactinemia results from a medication, that medication should be discontinued. If the hyperprolactinemia results from a pituitary tumor identified by an MRI, the adenoma can be treated with a dopamine agonist, such as cabergoline or bromocriptine. Resumption of normal spermatogenesis usually does not occur for at least three to six months.

In some patients who have a large pituitary tumor (macroadenoma), the hypogonadotropic hypogonadism appears to be the result of permanent damage to the gonadotroph cells by the mass effect of the adenoma. Lowering the serum prolactin concentration and reducing the tumor in this setting may not be sufficient to increase the testosterone concentration and sperm count. Thus, if the serum testosterone concentration does not increase to normal within six months of the serum prolactin being reduced to normal, gonadotropin treatment may be considered.

Removal of Gonadotoxic Agents

A wide range of chemical substances can affect sperm quality and/or quantity, including medications. The medications listed below are not exhaustive, but are commonly associated with male infertility and should be avoided:

- Anabolic steroids
- Antihypertensives
- Allopurinol
- Erythromycin
- Chemotherapy
- Cimetidine
- Colchicine
- Cyclosporine
- Dilantin
- Gentamycin
- Nitrofurantoin
- Tetracycline

Treatment with Human Chorionic/Menopausal Gonadotropin

Men who have hypogonadotropic hypogonadism due to hypothalamic disease can be treated with gonadotropin-releasing hormone (GnRH). Treatment is initiated with human chorionic gonadotropin (hCG), 1500 to 2000 IU three times per week subcutaneously or intramuscularly for at least six months; hCG has the biologic activity of LH. The hCG dose is adjusted upward according to symptoms of hypogonadism, serum testosterone concentrations, and semen parameters. Some patients with acquired hypogonadotropic states can be stimulated with hCG alone to produce sufficient sperm. If after six to nine months, the patient remains azoospermic or severely oligospermic, then human menopausal gonadotropin (hMG) or recombinant FSH may be added.

Pulsatile GnRH Treatment

Pulsatile subcutaneous or intravenous treatment with GnRH has also been successfully used to treat gonadotropin-deficient patients (40). GnRH has to be delivered in pulses using a portable pump with an attached catheter and needle for many months or years; most patients find it inconvenient to use GnRH therapy for so long.

Treatment of Genital Infections

Infertile men rarely present with symptoms or signs of acute genital infections or prostatitis, but they are sometimes diagnosed as having infections of the urogenital tract by the presence of increased leukocytes in the semen (41). Unfortunately, specific organisms are rarely identified. It is unclear if the leukospermia plays a pathogenic role in the infertility. The presence of leukocytes may decrease sperm functional capacity by the release of ROS. Semen cultures should be obtained when there are over one million leukocytes in the semen; however, the yield is usually poor and nondiagnostic.

Despite the absence of symptoms, patients who have leukospermia, even if the culture is negative, are treated with at least a 10-day course of antibiotics such as doxycycline or a quinolone. A second course of therapy is usually given if leukocytes persist in the semen after antibiotics. However, poor results make it difficult to demonstrate a cause and effect relationship between genital infections and male infertility. Exceptions are patients with a history of genital gonorrhea, tuberculosis, and other specific sexually transmitted diseases that lead to genital tract obstruction at the epididymis and vas deferens (42,43).

Treatment of Antisperm Antibodies

The presence of sperm antibodies on the sperm surface or in the seminal fluid can be determined by the immunobead test or mixed antiglobulin reaction (41). Glucocorticoids have been used in such patients. Continuous or intermittent high doses of prednisone for up to six months have been shown in placebo-controlled trials to improve pregnancy significantly (44).

However, there are adverse effects of high-dose corticosteroid therapy including aseptic necrosis of the femoral head. As a result, most couples attempt an ART such as ICSI.

Retrograde Ejaculation

Retrograde ejaculation (sperm backing up into the bladder) occurs in neurological conditions such as urogenital tract surgery, sympathetic denervation, and diabetes. IUI can be performed using semen collected after alkalinization of the urine and extensive washing of the sperm. The washed sperm can also be used for IVF or ICSI procedures. Concurrent use of alpha agonists, such as pseudoephedrine (Sudafed) beginning one week prior to producing a sample, may be helpful in closing the bladder neck and more occasionally, converting retrograde ejaculation to antegrade ejaculation.

Varicocele

Varicoceles are dilated veins of the scrotum that are commonly associated with diminished semen parameters. They are thought to have deleterious effects by increasing the temperature of the scrotum and potentially creating back pressure and toxins (45–47). Although the presence of varicoceles can be associated with normal semen parameters and normal fertility, many men with varicoceles have abnormal semen parameters including low sperm concentration, motility, and abnormal morphology. In a World Health Organization (WHO) study of over 9000 men who were partners in an infertile couple, a varicocele was much more common in men with abnormal semen (25.4% vs. 11.7% with normal semen) (45). When patients are carefully screened and the goals as well as the time frame to achieve pregnancy are clearly determined, varicocele repair may significantly improve semen parameters and thereby improve the success of conceiving naturally and/or with assisted reproduction.

Atrophic testes, elevated serum FSH levels, and/or severe oligospermia or azoospermia indicate severe damage and are associated with a diminished likelihood of fertility after varicocele ligation. A subinguinal approach has been shown to be effective treatment with low chance of adverse events. In some centers, laparoscopic varicocelectomy or vascular catheter embolization of spermatic veins are utilized (48). An alternative to varicocele ligation or embolization is an ART. Subfertile men with varicoceles should be offered repair with the understanding it may take anywhere from 3 to 12 months before there may be an improvement in semen parameters. Furthermore, couples may still require IUI or assisted reproduction in future depending on a variety of cofactors.

Obstructive Azoospermia

Obstructive azoospermia is determined by finding testes of normal size, normal serum FSH concentration, and absent sperm in the ejaculate. Both surgery and ART may be beneficial in such patients. As an example, obstruction of the epididymis or ejaculatory duct can be treated surgically. Azoospermia due to obstruction in the epididymis can be treated by surgical end-to-end anastomosis of the epididymal duct to the vas deferens. These procedures may lead to the presence of ejaculated sperm but the results are variable and depend on the site of connection (reanastomosis), the skill of the surgeon, and the duration of obstruction. Patients should have the opportunity to have sperm extracted and cryopreserved at the time of the reversal in the event they wish to proceed immediately with assisted reproduction, or in the event of reversal failure and obstruction.

The results are best when obstructive azoospermia is due to a vasectomy (49). The appearance of sperm after a vasectomy reversal can be over 85% with pregnancy in over 50% in selected patients. The success rate depends on the duration between vasectomy and the reversal procedure (Table 10.3) In general, the more time that has elapsed after a vasectomy, the poorer the pregnancy rates with reversal (50).

Ejaculatory duct obstruction presents with decreased semen volume and azoospermia or severe oligospermia. TRUS demonstrates dilated seminal vesicles, and aspiration of the seminal vesicles shows spermatozoa suggesting obstruction. This condition may be treated by transurethral resection (opening via the urethra) of the ejaculatory ducts with resulting improved semen quality and pregnancy in the partner (51,52).

Table 10.3 Patency and Pregnancy Rates for Vasectomy Reversals as a Function of Time

Time since vasectomy (yr)	Patency rate (sperm returning to the semen) (%)	Pregnancy rate (%)
<3	97	76
3–8	88	53
9–14	79	44
>15	71	30

ART can be combined to use sperm from men who have obstructive azoospermia to fertilize ova of their partners and achieve pregnancy. Sperm obtained by microsurgical aspiration from the epididymis (MESA) or from the testes by biopsy or fine-needle aspiration can be used with eggs aspirated from the female partner for IVF or ICSI (52,53). The fertilization rate of microsurgical sperm aspiration along with ICSI, despite epididymal or testicular sperm of low quality, is approximately 50%, and the pregnancy rate is about 40% per cycle and 20% per microsurgical aspiration (54).

For obstruction due to other epididymal lesions, or absent vas deferens, the results of surgical anastomosis are not as effective as those with aspiration and ICSI. Given the continuous improvements in sperm retrieval and ICSI techniques, surgical reversal versus ART must be discussed before an informed decision can be made (55).

Testicular Microdissection

New surgical techniques have been introduced to extract sperm from patients with nonobstructive azoospermia. A technique called microdissection of the testis to extract sperm (microTESE) from the seminiferous tubules has been successful in obtaining sperm in over 50% of patients with nonobstructive azoospermia, including patients with Klinefelter syndrome (56–58). Despite the chromosomal imbalance, the chance of transmission to an offspring is low.

Empirical Therapy

Many treatments have been used empirically for male infertility, including clomiphene citrate and other hormones as well as vitamins (59). However, when placebo-controlled prospective clinical trials have been performed with adequate numbers of subjects in randomized placebo-controlled trials, none of these methods (including clomiphene citrate and human recombinant FSH) has been proven effective in oligospermia or azoospermia of unknown etiology. Some data suggest that aromatase inhibitors (e.g., anastrazole) may improve sperm concentrations in men with severe oligospermia or azoospermia prior to sperm retrieval for ICSI (59,60).

Another recommendation often made to infertile men is to wear boxer undershorts instead of jockey style and not to take hot showers or baths. The rationale is that increased scrotal temperature may impair sperm production. However, a 12-month study of men who wore tight athletic supporters found a slight increase in scrotal temperature but no change in semen quality. The wearing of ordinary brief underwear had no effect on scrotal temperature compared to boxer-style underwear (61). Similarly, no change in semen parameters were found in men taking frequent saunas or hot baths.

Assisted Reproductive Techniques

ART is commonly used for the treatment of the female partner of men with severe oligospermia and azoospermia. IUI consists of washing an ejaculated semen specimen to remove prostaglandins, concentrating the sperm in a small volume of culture media, and injecting the sperm suspension directly into the upper uterine cavity using a small catheter through the cervix. The insemination is timed to take place just prior to ovulation. In couples with mild male infertility, IUI improves pregnancy rates when compared to intracervical insemination or timed natural cycles. However, in cases of moderate to severe oligospermia IUI treatments are rarely successful.

In Vitro Fertilization with Intracytoplasmic Sperm Injection

ICSI has revolutionized treatment and improved the prognosis for infertile men with severe oligospermia, asthenospermia (low sperm motility), teratospermia (a higher rate of abnormal sperm morphology), and even azoospermia. This technique involves the direct injection of a single sperm into the cytoplasm of a human oocyte, usually obtained from follicles produced under controlled ovarian hyperstimulation. This technique has also been successful in some men with Klinefelter syndrome where sperm are obtained from testicular biopsies (62,63). The overall fertilization rate is about 60% and the clinical pregnancy rate per cycle is about 20% while the multiple pregnancy rate is about 29% to 38%. The ICSI results are not influenced by either the cause of the azoospermia or the origin of the spermatozoa.

When there are no sperm in the ejaculate but there are sperm-producing cells (Sertoli cells) in the testes, ICSI can be performed with sperm isolated from testicular extraction (64,65). Success is dependent on retrieving adequate numbers of sperm. Successful pregnancy can occur using injection of fresh or cryopreserved (frozen) sperm, but not with spermatocytes (immature sperm). Extracted testicular sperm may fertilize oocytes even in azoospermic men with maturation arrest, defective spermatogenesis, Klinefelter syndrome, and in men with long-standing azoospermia after chemotherapy (66–70).

The ability of sperm from men with severe sperm abnormality and genetic disorders to fertilize human oocytes raises the issue of chromosomal abnormalities and congenital malformations in pregnancies from ICSI.

Artificial Insemination with Donor Semen

The alternative to ART for many couples is artificial insemination with donor sperm. This method has a very high success rate in otherwise normal females with close to 50% pregnancy rate within six cycles of insemination.

CONCLUSION

It is important to realize that infertility is often secondary to a male factor. In the past, men with infertility had relatively few options for treatment. In this era, however, it is often possible to clearly determine the etiology of male subfertility and provide treatment options that offer help to many couples. Men with abnormal semen parameters or other known infertility risk factors should have a urological evaluation.

REFERENCES

1. Thonneau P, Marchand S, Tallec A, et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod 1991; 6:811–816.
2. Honig SC, Lipshultz LI, Jarow J. Significant medical pathology uncovered by a comprehensive male infertility evaluation. Fertil Steril 1994; 62:1028–1034.
3. Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001; 345:1388–1393.
4. Kruger TF, Acosta AA, Simmons KF, et al. Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril 1988; 49:112–117.
5. Menkveld R, Stander FS, Kotze TJ, et al. The evaluation of morphological characteristics of human spermatozoa according to stricter criteria. Hum Reprod 1990; 5:586–592.
6. Pisarska MD, Casson, PR, Cisneros PL, et al. Fertilization after standard in vitro fertilization versus intracytoplasmic sperm injection in subfertile males using sibling oocytes. Fertil Steril 1999; 71:627–632.
7. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 2nd ed., Cambridge University Press, 1987.
8. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 3rd ed., Cambridge University Press, 1992.
9. Carter SS, Shinohara K, Lipshultz LI. Transrectal ultrasonography in disorders of the seminal vesicles and ejaculatory ducts. Urol Clin North Am 1989; 16:773–790.
10. Jarow JP. Transrectal ultrasonography of infertile men. Fertil Steril 1993; 60:1035–1039.
11. Coetzee K, Kruge TF, Lombard CJ. Predictive value of normal sperm morphology: a structured literature review. Hum Reprod Update 1998; 4:73–82.

12. Keegan BR, Barton S, Sanchez X, et al. Isolated teratozoospermia does not affect in vitro fertilization outcome and is not an indication for intracytoplasmic sperm injection. Fertil Steril 2007; 88:1583–1588.
13. Van Waart J, Kruger TF, Lombard CJ, et al. Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review. Hum Reprod Update 2001; 7:495–500.
14. Spiessens C, Vanderschueren D, Meuleman C, et al. Isolated teratozoospermia and intrauterine insemination. Fertil Steril 2003; 80:1185–1189.
15. Shibahara H, Obara H, Ayustawati , et al. Prediction of pregnancy by intrauterine insemination using CASA estimates and strict criteria in patients with male factor infertility. Int J Androl 2004; 27:63–68.
16. Gunalp S, Onculoglu C, Gurgan T, et al. A study of semen parameters with emphasis on sperm morphology in a fertile population: an attempt to develop clinical thresholds. Hum Reprod 2001; 16:110–114.
17. Evenson DP, Jost LK, Marshall D, et al. Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic. Hum Reprod 1999; 14:1039–1049.
18. Spano M, Bonde JP, Hjollund HI, et al. Sperm chromatin damage impairs human fertility. The Danish First Pregnancy Planner Study Team. Fertil Steril 2000; 73:43–50.
19. Evenson DP, Wixon R. Data analysis of two in vivo fertility studies using Sperm Chromatin Structure Assay-derived DNA fragmentation index vs. pregnancy outcome. Fertil Steril 2008; 90:1229–1231.
20. Duran EH, Morshedi M, Taylor S, Oehninger S. Sperm DNA quality predicts intrauterine insemination outcome: a prospective cohort study. Hum Reprod 2002; 17:3122–3128.
21. Bungum M, Humaidan P, Axmon A, et al. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. Hum Reprod 2007; 22:174–179.
22. Collins JA, Barnhart KT, Schlegel PN. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? Fertil Steril 2008; 89:823–831.
23. Zini A, Sigman M. Are tests of sperm DNA damage clinically useful? Pros and cons. J Androl 2009; 30:219–229.
24. Zini A, Boman JM, Belzile E, et al. Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: systematic review and meta-analysis. Hum Reprod 2008; 23:2663–2668.
25. Wolff H, Anderson DJ. Immunohistologic characterization and quantitation of leukocyte subpopulations in human semen. Fertil Steril 1988; 49:497–504.
26. Ayvaliotis B, Bronson R, Rosenfeld D, et al. Conception rates in couples where autoimmunity to sperm is detected. Fertil Steril 1985; 43:739–742.
27. Oei SG, Helmerhorst FM, Bloemenkamp KM, et al. Effectiveness of the postcoital test: randomised controlled trial. BMJ 1998; 317:502–505.
28. Liu de Y, Liu ML, Garrett C, et al. Comparison of the frequency of defective sperm-zona pellucida (ZP) binding and the ZP-induced acrosome reaction between subfertile men with normal and abnormal semen. Hum Reprod 2007; 22:1878–1884 [Epub 2007 Apr].
29. Anguiano A, Oates RD, Amos JA, et al. Congenital bilateral absence of the vas deferens. A primarily genital form of cystic fibrosis. JAMA 1992; 267:1794–1797.
30. Chillon M, Casals T, Mercier B, et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. New Engl J Med 1995; 332:1475–1480.
31. Hall S, Oates RD. Unilateral absence of the scrotal vas deferens associated with contralateral mesonephric duct anomalies resulting in infertility: laboratory, physical and radiographic findings, and therapeutic alternatives. J Urol 1993; 150:1161–1164.
32. Castellani C, Bonizzato A, Pradal U, et al. Evidence of mild respiratory disease in men with congenital absence of the vas deferens. Respiratory Medicine 1999; 93:869–875.
33. Gilljam M, Moltyaner Y, Downey GP, et al. Airway inflammation and infection in congenital absence of the vas deferens. Am J Respir Crit Care Med 2004; 169:174–179.
34. Schlegel PN, Shin D, Goldstein M. Urogenital anomalies in men with congenital absence of the vas deferens. J Urol 1996; 155:1644–1648.
35. Reijo R, Alagappan RK, Patrizio P, et al.: Severe oligozoospermia resulting from deletions of azoospermia factor gene on Y chromosome. Lancet 1996; 347:1290–1293.
36. Silber SJ, Repping S. Transmission of male infertility to future generations: Lessons from the Y chromosome. Hum Reprod Update 2002; 8:217–229.
37. Foresta C, Moro E, Ferlin A. Y chromosome microdeletions and alterations of spermatogenesis. Endocr Rev 2001; 22:226–239.
38. Schiff JD, Palermo GD, Veeck LL, et al. Success of testicular sperm extraction and intracytoplasmic sperm injection in men with Klinefelter syndrome. J Clin Endocrinol Metab 2005; 90:6263–6267.
39. Lanfranco F, Kamischke A, Zitzmann M, et al. Klinefelter's syndrome. Lancet 2004; 364:273–283.
40. Crowley WF Jr., Filicori M, Spratt DI, et al. The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. Recent Prog Horm Res 1985; 41:473–531.
41. World Health Organization. World Health Organization Laboratory Manual for the Examination of Human Semen and Sperm Cervical-Mucus Interaction. Cambridge: Cambridge University Press, 1999.

42. Hua VN, Schaeffer AJ. Acute and chronic prostatitis. Med Clin North Am 2004; 88:483–494.
43. Bar-Chama N, Goluboff E, Fisch H. Infection and pyospermia in male infertility. Is it really a problem? Urol Clin North Am 1994; 21:469–475.
44. Hendry WF, Hughes L, Scammell G, et al. Comparison of prednisolone and placebo in subfertile men with antibodies to spermatozoa. Lancet 1990; 335:85–88.
45. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril 1992; 57:1289–1293.
46. Saypol DC, Howards SS, Turner TT, et al. Influence of surgically induced varicocele on testicular blood flow, temperature, and histology in adult rats and dogs. J Clin Invest 1981; 68:39–45.
47. Mieusset R, Bujan L, Mondinat C, et al. Association of scrotal hyperthermia with impaired spermatogenesis in infertile men. Fertil Steril 1987; 48:1006–1011.
48. White RI. Radiologic management of varicoceles using embolotherapy. In: Whitehead ED, Nagler HM, eds. Management of Impotence and Infertility. Philadelphia: JB Lippincott, 1994:p. 228.
49. Southwick GJ, Temple-Smith PD. Epididymal microsurgery: current techniques and new horizons. Microsurgery 1988; 9:266–277.
50. Belker AM, Thomas AJ Jr., Fuchs EF, et al. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. J Urol 1991; 145:505–511.
51. Meacham RB, Hellerstein DK, Lipshultz LI. Evaluation and treatment of ejaculatory duct obstruction in the infertile male. Fertil Steril 1993; 59:393–397.
52. Jarow JP. Transrectal ultrasonography in the diagnosis and management of ejaculatory duct obstruction. J Androl 1996; 17:467–472.
53. Silber SJ, Ord T, Balmaceda J, et al. Congenital absence of the vas deferens. The fertilizing capacity of human epididymal sperm. N Engl J Med 1990; 323:1788–1792.
54. Silber SJ, Devroey P, Tournaye H, et al. Fertilizing capacity of epididymal and testicular sperm using intracytoplasmic sperm injection (ICSI). Reprod Fertil Dev 1995; 7:281–292.
55. Robb P, Sandlow JI. Cost-effectiveness of vasectomy reversal. Urol Clin North Am 2009; 36:391–396.
56. Donoso P, Tournaye H, Devroey P. Which is the best sperm retrieval technique for non-obstructive azoospermia? A systematic review. Hum Reprod Update 2007; 13:539–549.
57. Ramasamy R, Ricci JA, Palermo GD, et al. Successful fertility treatment for Klinefelter's syndrome. J Urol 2009; 182:1108–1113.
58. Schlegel PN. Nonobstructive azoospermia: a revolutionary surgical approach and results. Semin Reprod Med 2009; 27:165–170.
59. Schill WB. Survey of medical therapy in andrology. Int J Androl 1995; 18(suppl 2):56–62.
60. Kim HH, Schlegel PN. Endocrine manipulation in male infertility. Urol Clin North Am 2008; 35: 303–318.
61. Munkelwitz R, Gilbert BR. Are boxer shorts really better? A critical analysis of the role of underwear type in male subfertility. J Urol 1998; 160:1329–1333.
62. Palermo GD, Schlegel PN, Sills ES, et al. Births after intracytoplasmic injection of sperm obtained by testicular extraction from men with nonmosaic Klinefelter's syndrome. N Engl J Med 1998; 338:588–590.
63. Reubinoff BE, Abeliovich D, Werner M, et al. A birth in non-mosaic Klinefelter's syndrome after testicular fine needle aspiration, intracytoplasmic sperm injection and preimplantation genetic diagnosis. Hum Reprod 1998; 13:1887–1892.
64. Tournaye H, Camus M, Goossens A, et al. Recent concepts in the management of infertility because of non-obstructive azoospermia. Hum Reprod 1995; 10(suppl 1):115–119.
65. Schlegel PN, Palermo GD, Goldstein M, et al. Testicular sperm extraction with intracytoplasmic sperm injection for nonobstructive azoospermia. Urology 1997; 49:435–440.
66. Silber SJ, van Steirteghem A, Nagy Z, et al. Normal pregnancies resulting from testicular sperm extraction and intracytoplasmic sperm injection for azoospermia due to maturation arrest. Fertil Steril 1996; 66:110–117.
67. Chen SU, Ho HN, Chen HF, et al. Fertilization and embryo cleavage after intracytoplasmic spermatid injection in an obstructive azoospermic patient with defective spermiogenesis. Fertil Steril 1996; 66:157–160.
68. Mulhall JP, Reijo R, Alagappan R, et al. Azoospermic men with deletion of the DAZ gene cluster are capable of completing spermatogenesis: fertilization, normal embryonic development and pregnancy occur when retrieved testicular spermatozoa are used for intracytoplasmic sperm injection. Hum Reprod 1997; 12:503–508.
69. Tournaye H, Staessen C, Liebaers I, et al. Testicular sperm recovery in nine 47, XXY Klinefelter patients. Hum Reprod 1996; 11:1644–1649.
70. Chan PT, Palermo GD, Veeck LL, et al. Testicular sperm extraction combined with intracytoplasmic sperm injection in the treatment of men with persistent azoospermia postchemotherapy. Cancer 2001; 92:1632–1637.

11 Preimplantation genetic screening and diagnosis

Khanh-Ha D Nguyen, Alison E Zimon, and Kim L Thornton

Preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) are techniques that provide genetic and chromosomal information about developing embryos through biopsy and analysis of embryonic cellular material. PGD is a directed molecular diagnostic technique for a particular gene of interest, while PGS identifies those embryos with numerical chromosomal aberrations in couples at higher risk of aneuploidy. This technology is applicable and helpful to many couples seeking conception through IVF, particularly those with a known risk of transmitting single-gene disorders to their offspring or those at risk of generating embryos with structural or numerical chromosomal abnormalities. In couples using PGD and PGS, accurate and reliable determination of single-gene defects, chromosome structure, and chromosome number in blastomere or polar body biopsies is used to guide embryo selection prior to transfer. For many, this is a far more desirable option than awaiting fetal diagnosis in the first or second trimester of pregnancy via chorionic villus sampling or amniocentesis. While continuing to rapidly expand, PGS is offered to some couples to potentially enhance the chance of pregnancy and live birth for couples with repeated IVF failure (RIF), recurrent pregnancy loss, or advanced maternal age, although this application is still controversial.

TECHNIQUES

Embryo Biopsy

To perform PGD, cellular material for analysis can be obtained using one of three techniques: polar body biopsy of the oocyte prior to the completion of fertilization, blastomere biopsy three-day-old cleavage-stage embryos at the 6 to 10 cell stage, or trophectoderm biopsy of day-5 blastocysts.

Polar Body Biopsy

Polar body biopsy involves the removal of one or both of the polar bodies that are generated and extruded during the oocyte divisions that complete meiosis at ovulation and fertilization. Polar bodies may be safely removed following mechanical or chemical penetration of the zona pellucida surrounding the oocyte without disrupting the oocyte or embryo. Analysis of oocyte polar bodies strictly involves maternally derived genetic material and therefore paternally derived genetic or chromosomal abnormalities are not evaluated. In cases of maternally transmitted genetic disease or aneuploidy related to oocyte age, polar body PGD is 95% to 98% accurate.

Blastomere Biopsy

Blastomere biopsy of cleavage-stage embryos is the most commonly employed method to obtain genetic material for PGD. This is performed on day 3 of embryo development at the 6 to 10 cell stage when embryonic cells are totipotent and have not begun the process of compaction. One or two blastomeres if less than 25% of total embryo cellular material can be reliably removed from the embryo without compromising further development (Fig. 11.1). High error rates, noninformative biopsies, embryo damage from biopsy, and alterations in fluorescence in situ hybridization (FISH) conditions (e.g., over dehydration, fluctuation in osmolarity, staining temperatures, etc.,) highlight the importance of an experienced embryologist to produce reliable results. Removed blastomeres are subsequently analyzed for gene mutations or chromosomal abnormalities while the biopsied embryos continue to be observed in the laboratory. Once PGD results are available, normal embryos that have become blastocysts are selected for transfer on

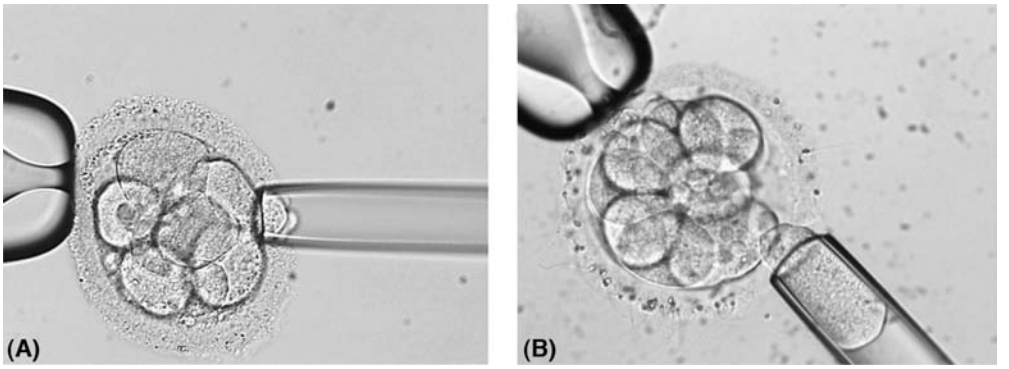

Figure 11.1 Performance of an embryo biopsy. (**A**) A small opening is created in the zona pellucid of a day-3 embryo. The biopsy pipette is positioned and then inserted through the opening. (**B**) A blastomere has been removed and is seen in the lumen of the pipette. *Source*: Courtesy of Mark Hughes, Genesis Genetics Institute, Detroit, MI.

day 5. Interestingly, not all blastomeres of a single embryo share identical chromosomal constitution, and this variance, termed mosaicism, poses an unavoidable limitation of blastomere analysis. Studies which have analyzed blastomeres from embryos at the cleavage stage with follow-up blastomere analysis at the blastocyst stage have confirmed that mosaicism may be present in upward of 50% of embryos. However, overall, it has been estimated that blastomere mosaicism contributes at most an error rate of 5%. Thus, PGD through blastomere biopsy is reliable and remains the current standard for preimplantation genetic analysis with a diagnostic efficiency of up to 95% to 98%. Laboratory expertise in embryo biopsy does vary and no diagnosis results may occur in up to 10% of cells biopsied.

Trophectoderm Biopsy

The final available method for embryo cellular analysis is trophectoderm biopsy of blastocyst embryos on day 5 of development. Here, the zona is penetrated chemically or mechanically, generating a fenestration through which several herniated trophectoderm cells are removed. However, this technique is limited and has not been applied extensively because a biopsy performed at this stage of development does not provide sufficient time for genetic analysis before transfer requiring freezing of all blastocyst-stage embryos after biopsy and the level of confined trophectoderm mosaicism is highly variable. Laboratory expertise to perform this biopsy is essential and technical differences between embryology labs may yield highly variable results for diagnosis, embryo survival, and pregnancy rates.

Genetic Analysis

Embryonic cellular material obtained via biopsy can be analyzed for specific gene sequences to diagnose single-gene defects through using polymerase chain reaction (PCR) or for chromosomal enumeration to screen for aneuploidy or chromosomal structural abnormalities using FISH, comparative genomic hybridization (CGH), or microarray of single nucleotide polymorphisms (SNPs).

Polymerase Chain Reaction

The PCR technique provides the ability to screen preimplantation embryos for single-gene defects with known mutation sequences. Following extraction of DNA from biopsied cells, oligonucleotide primers specific for the gene region of interest are used as the starting point for DNA replication by a temperature-specific polymerase. Through repeated specific temperature cycles, selected gene regions are amplified thereby providing sufficient DNA to determine whether the normal or mutated gene sequence is present. Challenges to optimizing this technique include the small initial amount of DNA available from embryo biopsy and the risk

of amplifying contaminating DNA. Nested PCR technique or simultaneous PCR amplification of different gene fragments by multiplex PCR are routinely used to enhance the reliability in this setting. Whole genome amplification by PCR can also be employed for analysis by CGH or SNP microarrays but can be especially sensitive to the same challenges of small initial genetic material and risk of contamination. In some cases, Y-chromosome amplification may not have as high fidelity as with other chromosomes and more stringent PCR conditions are necessary for accurate results. Allele dropout and partial amplification can lead to misdiagnosis and are major limitations of any PCR-based molecular technique.

Fluorescent In Situ Hybridization

The most commonly used method to analyze chromosomal integrity and number is FISH. Interphase chromosomes of biopsied cells can be detected, visualized, and counted by using fluorescent-tagged probes that interact and hybridize with the DNA (often the centromere) of the selected chromosomes of interest. Multiple chromosomes can be tested by using differently colored tags and performing repeated hybridization steps. Once hybridization is performed, the signals for each chromosome are counted and chromosomal euploidy or aneuploidy is determined. This technique can also be used to identify translocations or other chromosomal structural defects using probes specific to individual break points, q arms, or p arms. The inherent error rate for FISH can be reduced by repeating selective analysis with alternative probes in cases where an appropriate signal is lost or an artifact signal is detected.

Although FISH technology is a relatively simple procedure yielding rapid results in reasonable turnaround time (within a few hours if the PGD lab is associated with the embryology lab), it has several major disadvantages. First, there is a threshold number of chromosomes that can be tested in one cell due to interference of probe signals. Presently, it is standard to test only 9 to 12 of all 23 chromosome pairs. The chromosomes most often selected for testing by FISH are those with the highest observed incidence of aneuploidy in early embryos and pregnancy losses and include chromosomes X, Y, 8, 13, 14, 15, 16, 17, 18, 20, 21, and 22. Testing for even this limited panel of chromosomes would require two to three hybridization cycles and a maximum of 80% to 90% of aneuploidy would be detected. Second, prior belief that aneuploidy may be the cause of recurrent pregnancy loss, recurrent implantation failure, and poor pregnancy outcomes due to advanced maternal age was not confirmed in the early studies using PGS to improve pregnancy and live birth rates. The literature has been inconclusive; however, with newer CGH and SNP microarrays that examine all chromosome complements, more data is necessary to determine the ultimate application of PGS in these clinical settings. Finally, there is increasing evidence that embryos found to be aneuploid based on FISH of one blastomere on day 3 undergo "self-correction" in the process of developing into a blastocyst. This may occur if somatic mosaicism early in cleavage-stage embryos results in either low-level mosaicism that is undetectable by current methods or confined to the trophectoderm. In either scenario, the aneuploidy detected in day-3 embryos becomes less clinically significant; however, these embryos deemed to be abnormal at day 3 are discarded.

Comparative Genomic Hybridization

CGH is a recent technique that allows simultaneous and complete enumeration of chromosomes from a single biopsied cell without cellular fixation. In contrast to FISH, chromosomes are not directly visualized but the relative copy number of chromosome-specific probes between the test DNA and a control DNA is assessed after concurrent PCR amplification (Fig. 11.2). The technique is capable of screening biopsied cells for aneuploidy for individual chromosomes but may not differentiate balanced translocations unless there are subtle differences in DNA copy numbers that occasionally occur in these and other chromosomal structural rearrangements such as inversions. CGH also may not differentiate whole genome ploidy states such as polyploidy (e.g., 69,XX) or monoploidy (23,X) as there is equal representation of all chromosomes. Depending on the size of probes used (bacterial artificial chromosome or oligonucleotide), some clinically important microdeletion or microduplication disorders may also be detected. Presently, use of CGH is limited because the

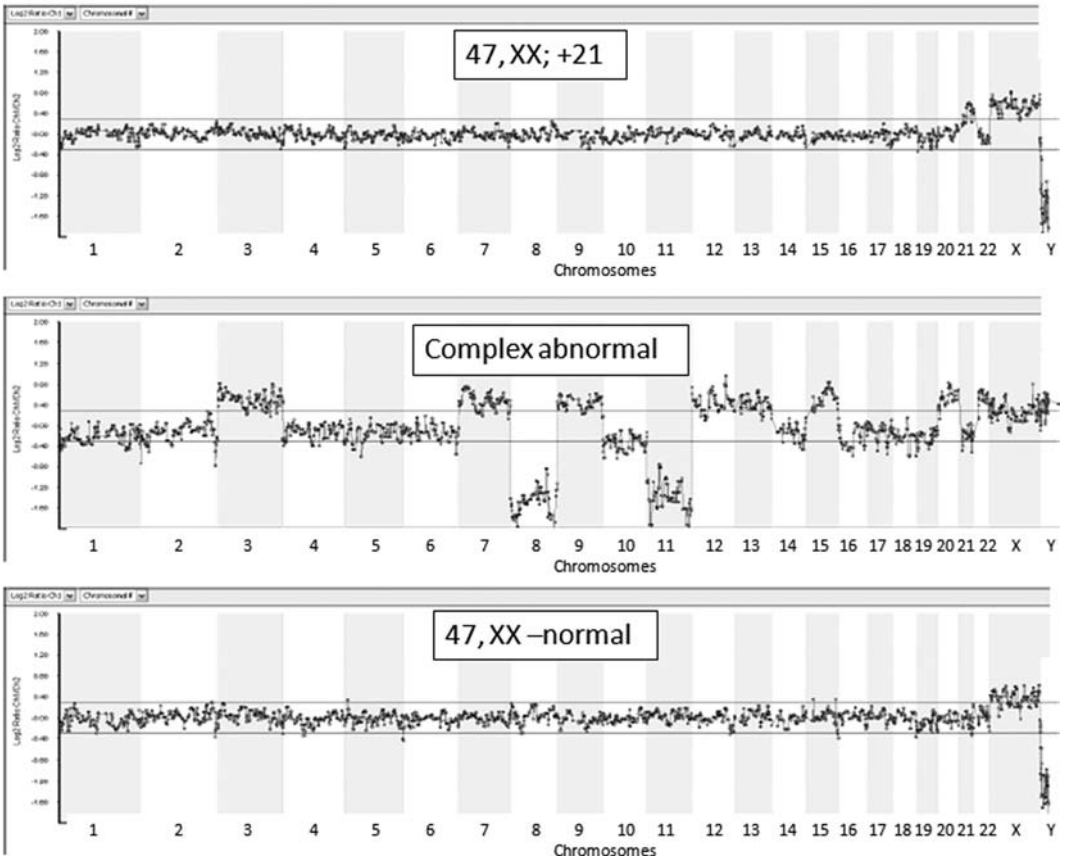

Figure 11.2 CGH results performed on biopsies taken from day-3 embryos. *Source*: Courtesy of Mark Hughes, Genesis Genetics Institute, Detroit, MI.

technique requires several days to perform. Since CGH cannot be completed during the window between biopsy and fresh transfer, embryos screened in this manner must be frozen during the diagnostic period and subsequently thawed and transferred in a later cycle once CGH results are available. Optimizing the technique and developing alternative methodologies, such as whole genome amplification with an isothermal polymerase and strand replacement, may ultimately shorten the procedural time required for CGH and render it more widely applicable clinically. While some centers are now able to generate reports in approximately 24 hours after receipt of the genetic material, overall time is still dependent on transport time between biopsy to the lab performing the analysis.

Single Nucleotide Polymorphism Microarray

SNPs are highly conserved variations at a single site in the DNA that exist in a frequency greater than 1% within a population. There are more than 10 million SNPs in the human genome making it a highly sensitive and specific genotyping marker for diagnosis. The microarray consists of a chip containing nucleotide acid sequences complementary to each SNP region of interest (density coverage may range from 100,000 to 1 million SNPs depending on the chip). The sample DNA obtained from PGD is amplified and hybridized to the chip. The hybridization signal detected can simultaneously provide information on DNA copy number important for aneuploidy screening and detection of clinically significant microdeletion and microduplications as well as determine parental origin, presence of uniparental disomy, and loss of heterozygosity. It is a powerful molecular tool with the same limitations of single-cell analysis; however, more labs are exploring the potential use of this technology for PGD and

PGS. Important to note again is that sensitivity of the assay, especially to detect low-level mosaicism, is variable with the most experienced labs reporting a threshold detection of 10% mosaicism.

INDICATIONS FOR PGD

As the technology for PGD advances, the indications for genetic evaluation of embryos prior to transfer are expanding. At present, PGD is routinely used for couples affected by or carrying alleles for known sex-linked diseases or autosomal single-gene defects. PGS is also commonly employed for patients at increased risk of chromosomal aneuploidy due to advanced ovarian age, chromosomal rearrangements, repeated implantation failure with IVF, and recurrent pregnancy loss. Evidence to support the routine use of PGS for these indications is still controversial.

Sex-Linked Diseases

Since original reports of successful PGD pregnancies in 1990, the technology has been widely used to screen embryos at risk for sex-linked disorders. For patients with or carrying sex-linked disorders, knowledge of the specific genetic mutation is not required as carrier or disease status can be deduced based on sex determination. X-linked recessive disorders are the most common of the sex-linked disorders and include hemophilia A and B, Duchenne and Becker's muscular dystrophy, adrenal leukodystrophy, X-linked ichthyosis, and Lesch–Nyhan syndrome, among others. Fathers affected by a sex-linked disorder have a 50% chance of passing on carrier status to daughters but cannot pass the disorder on to male offspring. Mothers carrying an X-linked disorder have a 50% chance of transmitting the disease state to male offspring and a 50% chance of transmitting the carrier state to female offspring. With the exception of Fragile X syndrome that occurs 1 in 3600 males and 1 in 4000 to 6000 females, X-linked dominant disorders are less common. Here, affected mothers have a 50% chance of passing the disease onto their offspring, whereas affected fathers can only pass the disease state to female offspring. Inheritance counseling in FMR1-related disorders such as Fragile X syndrome is particularly unique because less than 1% of cases are due to deletions, missense mutations, or RNA splicing defects and follow the X-linked dominant inheritance patterns. The rest of Fragile X syndrome cases are due to full expansions (>200) of CGG trinucleotide repeats inherited from a parent with the premutation (55–200 repeats). Expansion only occurs through inheritance of the affected maternal allele, that is, all mothers of affected individuals are premutation carriers. These women are at risk of having a child with the full mutation but they are also at increased risk of developing premature ovarian failure and Fragile X–associated tremor/ataxia syndrome (FXTAS). Male premutation carriers can only transmit the premutation to their offspring; however, all children will be carriers.

There are even fewer Y-linked disorders; however, they are especially significant in reproduction because they often involve male infertility. Preimplantation genetic diagnosis offers an option for these couples carrying sex chromosome–linked conditions to determine the sex of the embryo and transfer sex-selected embryos to avoid disease and/or carrier status in their children. Sex determination of biopsied embryos can be performed with PCR or FISH with excellent accuracy estimated at approximately 99%.

Single-Gene Defects

With the completion of the Human Genome Project, the sequence information for single-gene disorders has rapidly expanded allowing the application of PGD to detect disease or carrier status in embryos. Autosomal recessive disorders are more common and many have been successfully screened by PGD including cystic fibrosis, Tay–Sachs disease, sickle cell anemia, β-thalassemia, spinal muscular atrophy, and familial dysautonomia. Autosomal dominant disorders for which PGD has been applied include Huntington's disease, neurofibromatosis, retinitis pigmentosa, Marfan's syndrome, and familial adenomatous polyposis coli. Among the challenges of preimplantation diagnosis of monogenic diseases is the ability to screen for the various mutations leading to disease. For example, cystic fibrosis can be caused by over 1000 known mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene of

Table 11.1 Most Common Genetic Disorders Evaluated by PGD

Achondroplasia (FGFR3)
Adrenoleukodystrophy (ABCD1)
Agammaglobulinemia-Bruton (TyrsKnse)
α-Thalassemia (HBA1)
α-Antitrypsin (AAT)
Alport syndrome (COL4A5)
Alzheimer disease (very early onset PSEN1)
β-Thalassemia (HBB)
Bloom syndrome (Blm)
Canavan disease (ASPA)
Charcot-Marie-Tooth Neuropathy—2E
Charcot-Marie-Tooth Neuropathy—1B
Choroideremia (CHM)
Chronic granulomatous disease (CYBB)
Citrullinemia (ASS)
Cleidocranial dysplasia (RUNX2)
Congenital adrenal hyperplasia (CYP31A2)
Congenital erythropoietic porphyria (UROS)
Crigler–Najjar syndrome (UGT1A1)
Cystic fibrosis (CFTR)
Darier disease (ATP2A2)
Diamond–Blackfan anemia (DBA-RSP19)
Diamond–Blackfan anemia (DBA2)
Duchenne muscular dystrophy (DMD)
Dystrophy myotonica (DMPK)
Emery–Dreifuss muscular dystrophy (EDMD1,2,4)
Epidermolytic hyperkeratosis (KRT10) factor 13 Deficiency (F13A1)
Familial adenomatous polyposis (APC)
Familial dysautonomia (IKBKAP)
Fanconi anemia A (FANCA)
Fanconi anemia C (FANCC)
Fanconi anemia F (FANC F)
Fanconi anemia G (FANCG)
Fragile X syndrome (FMR1)
Friedreich ataxia I (FRDA)
Gaucher disease (GBA)
Glutaric acidemia type 1 (GCDH)
Hemophilia A (F8)
Hemophilia B (F9)
HLA DR beta1 class II MHC (HLA DRB1)
HLA-A class I MHC (HGNC HLA-A)
Hunter syndrome (IDS)
Huntington disease (HD)
Hurler syndrome (MPSI-IDUA)
Hyper IgM (CD40-ligand; TNFSF5)
Hypophosphatasia (ALPL)
Incontinentia pigmenti (KBKG-NEMO)
Kennedy's disease (AR)
Krabbe disease (GALC)
Lesch–Nyhan (HPRT1)
Leukemia, acute lymphocytic (for HLA)
Leukemia, acute myelogenous (for HLA)
Leukemia, chronic myelogenous (for HLA)
Leukocyte adhesion deficiency (ITGB2)
Li-Fraumeni syndrome (TP53)
Lymphoproliferative disorder (X-linked)
Marfan syndrome (FBN1)
Menkes disease (ATP7A)
Metachromatic leukodystrophy (ARSA)
Mucolipidosis 2 (I-Cell)
Neurofibromatosis (NF1 & NF2)
Niemann–Pick disease type C (NPC1)
Ornithine transcarbamylase deficiency (OTC)
Osteogenesis imperfecta (COL1A1)
Pachyonychia congenita (KRT16 & KRT6A)
Periventricular heteropia (PH)
Polycystic kidney disease, autosomal recessive (AR-PKD1)
Retinoblastoma 1 (RB1)
Rhesus blood group D (RHD)
Rhizomelic chondrodysplasia puncta (RCDP1)
Sacral agenesis (HLXB9)
Sanfilippo A disease (MPSIIIA)
SCID-X1 (severe combined immunodeficiency disease) (IL2RG)
Sexing for X-linked disease (AMELX/Y; ZFX/Y)
Shwachman–Diamond syndrome (SBDS)
Sickle cell anemia (HBB)
Smith–Lemli–Opitz syndrome (SLOS)
Spinal muscular atrophy (SMN1)
Spinocerebellar ataxia-3 (SCA3)
Spinocerebellar ataxia-2 (SCA2)
Tay–Sachs Disease (HEXA)
Treacher–Collins syndrome (TOCF1)
Tuberous sclerosis 1 (TSC1)
Wiskott–Aldrich syndrome (WAS)

which 25 are routinely tested. With known sequence and mutation data, fluorescent and multiplex PCR can provide accurate diagnostic screening of biopsied embryo cells with an error rate of less than 5% (Table 11.1). Despite the applicability of PGD for single-gene defects, it is still the standard of care to test parents for carrier status using conventional techniques and testing for that specific mutation in the offspring.

Aneuploidy

Even in the best-prognosis patients, pregnancy success per cycle of IVF is at best 40% to 50% and the chance of miscarriage is 15% to 20%. The overwhelming majority of failed implantations and pregnancy loss is due to chromosomal nondisjunction resulting in nonviable aneuploid embryos. In part because human oocytes are arrested in meiosis for the duration of a woman's life until the time of conception, it is believed that the chromosomal spindle apparatus and the chiasmata-adhering paired chromosomes are particularly vulnerable to damage accumulating with age. Oocyte aneuploidy is therefore perhaps the greatest

limitation of human reproduction and at present there are no potential methods to prevent or reverse this phenomenon. Unfortunately, the current grading of embryos by morphological analysis does not correlate with chromosomal status, and neither this nor any other noninvasive method can accurately predict euploid or aneuploid status in early embryos. PGS for chromosomal enumeration using FISH is therefore a valuable technology to select chromosomally normal embryos prior to transfer.

While polar body biopsy evaluates only the maternal chromosomal contribution to the embryo, it is estimated that 90% of aneuploidy in embryos is maternal in origin and therefore polar body analysis can be used as a reliable approach. However, PGS of blastomere biopsies is favored by most fertility centers as both the paternal and maternal contribution is assessed and the analysis can be completed by day 5 of development to allow for blastocyst transfer. The current common indications for PGS include advanced maternal age, RIF, and recurrent pregnancy loss; however, a consensus regarding the attributable benefit of this screening in each of these conditions has not yet been established. Large randomized controlled trials to determine if PGS by FISH could improve live birth rates have overall shown increased pregnancy rates but no change in live birth rates. Because of this the European Society of Human Reproduction and Embryology (ESHRE) has established guidelines for the responsible use of PGS: (*i*) PGS may have more potential benefit for those of advanced maternal age greater than 37 years old; (*ii*) PGS should only be performed if there are at least six embryos of normal morphology; (*iii*) only highly experienced embryologists should perform the biopsies; and (*iv*) limitations of FISH and availability of 24-chromosome screening make CGH or SNP microarrays the more desirable molecular approach. Similarly, the Practice Committee of American Society for Reproductive Medicine (ASRM) concluded after extensive review of the available literature in 2008 that there is insufficient evidence to advocate PGS by conventional FISH technology to improve live birth rates in women of advanced maternal age. As more data is generated using CGH and SNP microarrays, reevaluation of preimplantation genetic testing for aneuploidy screening may yield more accurate and comprehensive results.

Advanced Maternal Age

As aneuploidy increases with maternal age, aneuploidy screening by PGS is an option for women of advanced reproductive age, generally considered to be 35 years and older. The original retrospective studies examining the effect of PGS on aneuploidy screening demonstrated a significant increase in implantation rate and decreased miscarriage rate. Randomized controlled and multicenter trials in the United States have been criticized for their insufficient power and confounding variables, such as the type of biopsy technique, number of blastomeres removed, day of transfer, and low overall implantation rates. The largest and most strictly designed study examining the impact of PGS aneuploidy screening is a randomized control trial based in Belgium which failed to demonstrate a statistically significant difference in implantation, ongoing pregnancies, or pregnancy losses in 148 PGS subjects and 141 control subjects undergoing blastocyst transfer without PGS. Significantly fewer embryos were transferred in the PGS group and, though not statistically significant, the twin gestation rate was lower in the PGS group. While further data examining the clinical impact of PGS aneuploidy screening is forthcoming, couples may find the added assurance of embryo chromosomal status invaluable for decisions regarding selection of embryos for transfer and cryopreservation.

Recurrent Pregnancy Loss

For couples with two or more previous spontaneous abortions, screening for aneuploidy, together with chromosomal translocations, may provide valuable information, enhance pregnancy success, and decrease pregnancy loss. On the basis of PGS studies in patients with a prior history of an aneuploidy loss, the risk of subsequent aneuploidy is increased, particularly in women aged less than 35 years. For those women with recurrent pregnancy loss without aneuploidy, the data is less clear. In women with recurrent loss and advanced maternal age greater than 40 years, the potential benefits are also variable due to the decreased

yield of embryos developing beyond day 3 and extremely high rate of aneuploidy in surviving embryos.

Repeated IVF Failure

Similar to recurrent pregnancy loss, it is presumed that a significant contributing etiology to failed IVF in poor-prognosis patients is chromosomal aberrations. Some studies using CGH suggest patients with RIF have more complex abnormalities. It has been difficult to compare studies because of wide variation in definition and molecular technique used for screening. Mean aneuploidy rates may be as high as 70% in embryos of these couples. Randomized controlled trials of PGS in the setting of RIF only employed seven- to nine-probe FISH and there was no significant difference between PGS and control groups in implantation or clinical pregnancy rates. Patients should be counseled on the inconclusive benefit of PGS in RIF if PGS is offered as a treatment option.

Chromosomal Translocations

PGS is also beneficial in couples where a parental chromosomal translocation is discovered during the evaluation for recurrent pregnancy loss or infertility. Patients who are carriers of balanced translocations or inversions are predisposed to having a higher proportion of chromosomally abnormal gametes. PGS may benefit in cases of specific types of rearrangements, for example, if the involved chromosomes are of greatly disparate sizes. Paracentric inversions only yield 50% viable gametes but these are balanced whereas pericentric inversions produce 100% viable gametes with 50% of them unbalanced. In this situation, PGS for pericentric inversion carriers may decrease miscarriage rates from aneuploidy and delivery of a child with an unbalanced karyotype. Reciprocal translocations result in one-third gametes with normal complement. The risk of unbalanced offspring in Robertsonian translocations (those involving acrocentric chromosomes) depends on the sex of the carrier parent and the chromosomes involved. Although data is not extensive, in one report of nearly 500 patients undergoing PGS for parental Robertsonian and reciprocal translocations the loss rate was significantly reduced to 2% with an overall probability of pregnancy of 20% to 36%. Genetic counseling is crucial prior to proceeding with PGD or PGS to determine the true risk in all these clinical scenarios.

CONTROVERSIAL TOPICS

Several important concerns have arisen from PGD/PGS technology. Ethical debates have been especially fierce in cases when PGD is used to select human leukocyte antigen (HLA)-compatible embryos to help treat a sibling affected by a disease amenable to cure with transplantation. Some patients struggle with decisions to donate unaffected non-HLA-matched embryos to other couples or for research, or to discard them. Since the beginning of PGD, there have been precedent cases questioning if "designer" babies can morally be used for treatment of their older siblings and if parents can have sound conscience by not attempting every option available especially in situations when fatality would otherwise be inevitable.

Unique situations involving nondisclosure of parental genotype may occur if a parent at risk of an adult-onset disorder desires unaffected offspring without knowing his/her carrier status. While this is relatively infrequent, it has clear implications on expenses and risks involved in undergoing potentially unnecessary procedures in one or more IVF cycles for the emotional or mental benefit of the patient who does not desire to know his/her genotype.

Treatment for young cancer patients has improved dramatically. Patients with adult-onset cancers such as Li-Fraumeni syndrome, Von Hippel–Lindau syndrome, and BRCA-related breast cancers can look forward to longer survival. Longer survival and improved quality of life for these patients translate into realistic expectations to become parents. Although the American College of Medical Genetics has clear guidelines on when persons at risk of developing one of these disorders should be tested, PGD to screen for carrier embryos is very controversial because transmission penetrance of most of these disorders is often less than 100%. Although it is not known which carrier embryo will ultimately develop the disease later

in life, it is more acceptable for some parents to select against these embryos as their disease status may bias their decisions.

Finally, there were some early concerns regarding increased risk of congenital anomalies in embryos subjected to PGD techniques. Current data from the ESHRE PGD Consortium and over 1000 cases in a large PGD program in Chicago do not suggest increased rates of congenital anomalies overall or in any one organ system. These groups continue to collect data on live born infants resulting from PGD so that individual groups can be more closely examined, such as patients with or without infertility history, embryos that required ICSI, those embryos undergoing cryopreservation, and patients with prior poor IVF outcomes.

FUTURE PGD INDICATIONS

Recent data from PGD performed in healthy and young egg donors indicates that the ratio of aneuploid to normal embryos is high, approximating more than 30%. These data have led some clinicians to consider whether couples using oocyte donation may benefit from PGD analysis. As more outcome data become available, it is possible that PGD may be more widely applied to assess chromosomal status in donor cycles and perhaps all cycles in the future.

SELECTION AND COUNSELING OF PATIENTS WHO MAY BENEFIT FROM PGD/PGS

Clinicians can best identify those patients who are likely to benefit from PGD/PGS by obtaining a thorough genetic and obstetric history. Patients who may have or carry single-gene defects may have a history of genetic disease in a family member or a family history of unexplained pregnancy losses or neonatal deaths. A couple's family history may also reveal specific ethnicities that are associated with increased rates of genetic disease, such as the association between sickle cell anemia and African-American heritage or the association between cystic fibrosis and Northern European or Ashkenazi Jewish heritage. Couples with recurrent pregnancy loss or recurrent implantation failure are at increased risk of carrying and chromosomal translocation and would benefit from PGS. Women with poor pregnancy or IVF outcomes or those of advanced maternal age are more likely to produce aneuploid embryos and therefore should also be offered PGS.

It is our policy that all couples undergoing PGD/PGS meet with a genetic counselor so they have a complete understanding of the genetic disorder of concern, as well as the limitations of PGD/PGS. When counseling couples, it is also important that they be made aware of alternative options including donor gametes. For those couples at risk of chromosomal or genetic abnormalities who do not undergo PGD/PGS and do become pregnant, prenatal diagnosis can be performed later in pregnancy by chorionic villus sampling (CVS) at 12 to 14 weeks or amniocentesis at 16 to 20 weeks. Those couples who desire preimplantation testing should also be made aware of the inherent limitations of the testing due to a baseline error rate depending on the molecular technique used, the contribution of embryonic mosaicism, and the possibility of a reduced overall embryo yield per cycle. In addition, the ASRM guidelines for proper counseling of patients who choose preimplantation genetic testing include discussion of risks associated with IVF and embryo biopsy, genetic counseling regarding inheritance and expected outcomes based on diagnosis desired (single testing or tiered diagnosis with HLA testing, single-gene detection, and/or sex selection), alternatives to preimplantation testing such as CVS, amniocentesis, options of donor gamete, and disposition of undesired embryos (affected and unaffected). Further, if pregnancy is achieved following PGD/PGS we strongly recommend a CVS or amniocentesis to confirm the diagnosis.

CONCLUSIONS

In summary, PGD and PGS is a rapidly expanding technological advance and may greatly benefit couples at risk for transmitting genetic or chromosomal abnormalities to their offspring. As more published data becomes available, it is likely that the use of PGD and PGS will become more widespread and may prove to be beneficial to more if not all couples using ART.

RECOMMENDED READING

American Society for Reproductive Medicine. Preimplantation Genetic Testing: A Practice Committee Opinion. Fertil Steril 2008; 90:S136–S143.

Baart EB, Martini E, van den Berg I, et al. Preimplantation genetic diagnosis reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF. Hum Reprod 2006; 21:223–233.

Braude P, Pickering S, Flinter F, et al. Preimplantation genetic diagnosis. Nat Rev 2002; 3:941–953.

Carp HA, Dirnfeld M, Dor J, et al. ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy? Hum Reprod 2004; 19:1502–1505.

Kuliev A, Verlinsky Y. Place of preimplantation diagnosis in genetic practice. Am J Med Genet 2005; 134A:105–110.

Munne S, Chen S, Fischer J, et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriage. Fertil Steril 2005; 84:331–335.

Northrop LE, Treff NR, Levy B, et al. SNP microarray-based 24 chromosome aneuploidy screening demonstrates that cleavage-stage FISH poorly predicts aneuploidy in embryos that develop to morphologically normal blastocysts. Mol Hum Reprod 2010; 16:590–600.

Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. The Lancet 2004; 363:1633–1641.

Simpson JL. Preimplantation genetic diagnosis at 20 years. Prenat Diagn 2010; 30:682–695.

Staessen C, Platteau P, Van Assche E, et al. Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. Hum Reprod 2004; 19:2849–2858.

12 Polycystic ovary syndrome

Rita M Sneeringer and Vasiliki A Moragianni

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-age women and the most frequent cause of anovulatory infertility. As a syndrome, it is a collection of specific signs and symptoms rather than a well-defined disorder. As such, it can include variable clinical presentations. Depending on the criteria used for diagnosis, the prevalence ranges from 9% to 18% (1). The etiology remains largely unknown. PCOS is associated with long-term health complications, including diabetes, obesity, heart disease, and endometrial hyperplasia or cancer. Accurate diagnosis allows for directed treatment and prevention of comorbidities. Diagnostic criteria, clinical presentation, potential pathophysiology, and evidence-based treatments are summarized here.

DIAGNOSIS

Stein and Leventhal first described the syndrome of PCOS in 1935 as the combination of polycystic ovaries and amenorrhea. Since then, the definition and hence diagnosis of PCOS has evolved. Much controversy exists due to the varied presentation. In the past decades, several different diagnostic criteria have been developed for the classification of PCOS (Table 12.1). The initial diagnostic criteria were developed during a consensus meeting at the National Institutes of Health (NIH) in 1990. The NIH criteria required both chronic anovulation as well as clinical and/or biochemical signs of hyperandrogenism (2). Notably, polycystic ovaries were not required for the diagnosis of PCOS. In 2003, a consensus workshop held jointly by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam revised the diagnostic criteria. For the Rotterdam criteria, two out of the following three symptoms are required: oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (3). The Rotterdam criteria broadened the clinical spectrum of PCOS by including two additional groups of women who did not previously meet the NIH definition: women with only hirsutism and polycystic ovaries, but regular menstrual cycles; and women with oligomenorrhea and polycystic ovaries, but without hyperandrogenism. Finally, in 2006, the Androgen Excess Society (AES) Task Force developed consensus guidelines that placed a greater emphasis on the elevated androgens that characterize this syndrome. In the AES criteria, PCOS can be diagnosed following documented hyperandrogenism (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-ovulation and/or anovulation and/or polycystic ovaries) (4). Women with ultrasound appearance of polycystic ovaries and ovulatory dysfunction in the absence of hyperandrogenism would not meet the AES criteria for the diagnosis of PCOS. Further, the AES and NIH criteria are quite similar with some minor modifications to include women with hyperandrogenism and polycystic ovaries in the absence of menstrual irregularity.

Importantly, all three diagnostic criteria require the exclusion of other etiologies of menstrual irregularities and hyperandrogenism. Possible other diagnoses include adrenal or ovarian androgen-secreting neoplasm, hyperprolactinemia, syndromes of severe insulin resistance, thyroid dysfunction, congenital adrenal hyperplasia, Cushing's syndrome, and acromegaly. Typically, the measurement of thyroid-stimulating hormone, prolactin, glucose, insulin, and an androgen panel [DHEA-S (dehydroepiandrosterone sulfate), testosterone, and 17-OH progesterone] is sufficient to exclude other major causes if normal levels are noted. Specific testing for Cushing's syndrome and acromegaly is done if suspected based on history or phenotypic changes noted on physical exam (e.g., striae, round face, dorsal fat pad, central obesity, uncontrolled hypertension, increased glove or shoe size). For patients that have either severe or rapid onset of hyperandrogenic symptoms, an alternative diagnosis should be suspected as this is atypical for PCOS. Virilization (clitoromegaly, male-pattern frontal balding, or increased musculature) may also suggest tumor development. An androgen-secreting

Table 12.1 Diagnostic Criteria for PCOS and Associated Variable Phenotypes

Criteria	Hyperandrogenism (clinical or biochemical)	Menstrual irregularity/ anovulation	Polycystic-appearing ovaries on ultrasound
NIH	✔	✔	
Rotterdam	✔	✔	
	✔		✔
		✔	✔
	✔	✔	✔
Androgen Excess Society	✔	✔	
	✔		✔
	✔	✔	✔

tumor would typically contribute to serum testosterone levels greater than 150 to 200 ng/dL or DHEA-S levels above 700 μg/dL in premenopausal women. Congenital adrenal hyperplasia is suspected if 17-OH progesterone level is elevated. Further assessment with an ACTH stimulation test should be performed when a morning 17-OH progesterone level performed in the follicular phase is >200 ng/dL.

Additional testing that is consistent with the diagnosis of PCOS, but is not part of any criteria, includes an elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio (>3:1) and hyperinsulinemia. These factors have been linked to PCOS, possibly secondary to underlying etiology (see below), but are not necessary for the diagnosis of PCOS. It is also important to emphasize that PCOS is a syndrome, a collection of features rather than a definitive disease that may actually represent multiple underlying disorders.

CLINICAL PRESENTATION AND EVALUATION

Patients with PCOS usually present to care for three primary reasons: menstrual disturbances, hyperandrogenism, and infertility. Additional hallmarks of PCOS include obesity and metabolic disorders such as diabetes. There can also be a strong family history. A few distinct subgroups may present without the "typical phenotype" including women with lean PCOS and adolescents. The clinical characteristics of PCOS and suggested evaluation are described here (Table 12.2).

Menstrual disturbances are found in the majority of PCOS patients and are required for diagnosis if using the NIH criteria. The type of menstrual disorder can vary, but the underlying etiology is the same, anovulatory cycles. Most patients present with oligo-ovulation or anovulation leading to oligomenorrhea or amenorrhea. However, some women appear to have spontaneous menses with abnormal flow. This excessive bleeding could be the result of an absent luteal phase causing heavy, prolonged bleeding due to unopposed effects of estrogen. Thus, for women who have any irregularity of their menses (cycles <21 days or >35 days, highly variable cycle length, or abnormal flow), PCOS is a potential diagnosis. Additional testing, such as a luteal progesterone level, can help to determine if cycles are anovulatory. A progesterone level of >3 ng/mL is confirmatory of ovulation.

Ultrasound assessment may reveal polycystic ovaries that are associated with chronic anovulation and can be a sign of the ovarian dysfunction in PCOS (incorporated in the Rotterdam and AES criteria). However, this finding is not specific and can be seen in patients with multiple etiologies for anovulation. Further, polycystic ovaries can be a normal isolated finding in approximately one-third of ovulating women without metabolic sequelae typical for PCOS (5). Therefore, it is important to correlate the presence of polycystic ovaries with other clinical findings. The specific parameters for the diagnosis of PCO-appearing ovaries are as follows: ≥12 follicles in each ovary that measure 2 to 9 mm or ovarian volume ≥10 cc (Fig. 12.1). The evaluation is not valid if a dominant follicle is present.

Hyperandrogenism is the other major component of PCOS. Hirsutism (excessive hair growth) is the primary clinical indicator of hyperandrogenism but its diagnosis is subjective and ethnicity-dependent (6,7). A standardized scoring system, such as the Ferriman–Gallwey

Table 12.2 Suggested Evaluation of PCOS/Chronic Anovulation

History and Physical
Menstrual history, galactorrhea
BMI, blood pressure, waist circumference, hirsutism, acanthosis nigricans, thyroid striae, round face, dorsal fat pad, hypertension, central obesity (Cushing's symptoms)
Enlarged hands and feet, prominent facial features (acromegaly)
Confirm the diagnosis of PCOS
Ultrasound of the ovaries and endometrial stripe
Androgens (mildly elevated) and sex hormone–binding globulin
Consider luteal progesterone
Exclude other endocrinopathies/causes of chronic anovulation
hCG (pregnancy)
Total testosterone (ovarian/adrenal tumor)
DHEA-S (adrenal tumor)
Morning 17-OH progesterone (congenital adrenal hyperplasia)
FSH/LH (ovarian failure)
TSH (thyroid disorder)
Prolactin (hyperprolactinemia)
Dexamethasone suppression test (Cushing's syndrome, only if suspected)
IGF-1 (acromegaly, only if suspected)
Evaluate for comorbidities of PCOS
HgbA1C (diabetes/glucose intolerance)
Endometrial biopsy for prolonged anovulation (endometrial hyperplasia/cancer)
Lipid profile (hyperlipidemia, metabolic syndrome)

Abbreviations: PCOS, polycystic ovary syndrome; hCG, human chorionic gonadotropin; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

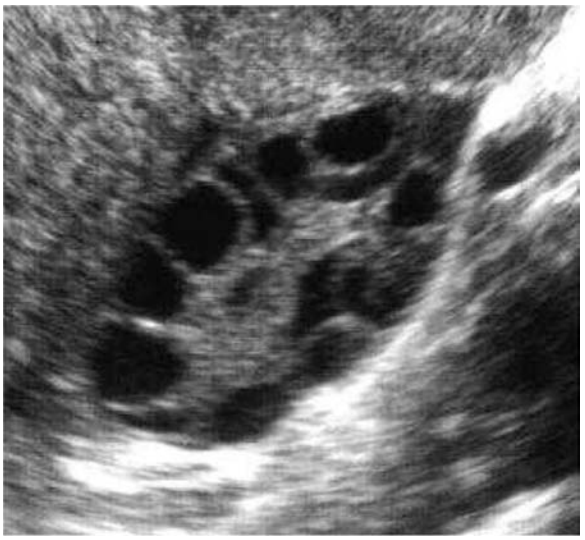

Figure 12.1 PCO morphology parameters: >12 follicles per ovary that measure 2 to 9 mm or ovarian volume $\geq$10 cc. The ultrasound evaluation is not valid if a dominant follicle is present. PCO morphology can be seen in only one ovary. PCO morphology alone is *not* sufficient for the diagnosis of PCOS and can be a normal finding in 20% of fertile women. *Abbreviation*: PCOS, polycystic ovary syndrome.

score, can be a helpful tool in evaluating hirsutism (Fig. 12.2). This scale assesses the density and distribution of hair growth on multiple areas of the body. Generally, a summation score of greater than 8 is consistent with hirsutism. Other, less specific, clinical features of hyperandrogenism include acne, oily skin, and male-pattern alopecia. Biochemical markers of hyperandrogenism include elevated testosterone or DHEA-S levels.

In addition to the diagnostic symptoms, many patients with PCOS have metabolic abnormalities that should be recognized in order to mediate future health risks. Insulin resistance, and hence hyperinsulinemia, is an important finding in many PCOS patients and is

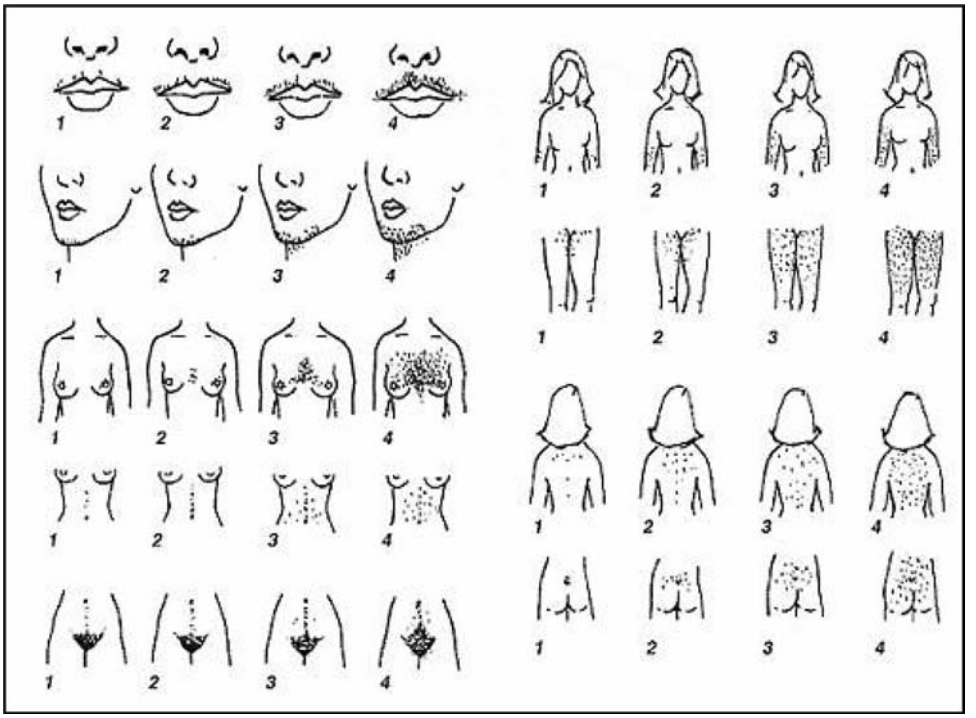

Figure 12.2 Ferriman–Gallwey Score for the clinical assessment of hirsutism. A summation score of 8 is consistent with hirsutism. *Source*: From Ref. 15.

suspected particularly among patients with acanthosis nigricans on physical exam. Acanthosis nigricans is a pigmented, velvety skin lesion that is noted most commonly on the back of the neck, axilla, and groin. PCOS patients are at an increased risk for glucose intolerance or diabetes with up to 45% of patients affected (8) and approximately 16% of patients developing glucose intolerance annually (9). Centripetal obesity is found in the majority of patients with PCOS and is considered part of the typical phenotype. It likely exacerbates risk of other comorbidities. The metabolic syndrome characterized by abdominal obesity, hypertension, high triglycerides, inflammatory factors, and increased thrombophilic factor is twice as likely to occur in patients with PCOS and is associated with an increased risk of cardiovascular disease (10). Clearly, these associated metabolic conditions have significant long-term consequences and all patients with PCOS should be screened with regular assessment of glucose tolerance testing, blood pressure, waist/hip measurement, body mass index, and lipid panel (including triglycerides, total cholesterol, and HDL).

Reproductive potential is impacted greatly by anovulation. Issues of subfertility and infertility are central to the presentation of PCOS patients, as are concerns about pregnancy outcomes and health risks to their offspring. The precise risks of infertility and spontaneous abortion rates are controversial with varying degrees of risk reported in multiple studies. Some increased risk is likely, especially among obese patients, manifesting as increased time to conception, reduced efficacy of infertility treatments, and increased risk of miscarriage. In addition, obstetric risks, including pregnancy-induced hypertension and gestational diabetes, are increased among patients with PCOS.

A higher incidence of endometrial abnormalities secondary to chronic anovulation is found in some patients with PCOS. Hyperplasia can occur and rarely endometrial cancer is encountered. Pathology evaluation of the endometrium is warranted in anovulatory patients regardless of age. However, an endometrium of <5 mm noted on vaginal ultrasound exam is rarely associated with endometrial hyperplasia and therefore an endometrial biopsy is not necessary in this circumstance.

PCOS can be associated with a significant psychological impact that is often overlooked. The feminine identity and body image are primarily affected, as patients suffer from obesity, acne, oily skin, excess hair growth, not to mention infertility and several other health care issues. The data is limited but evidence exists that PCOS patients are more prone to also develop several psychiatric disorders, including major depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction (11,12). As a result, patients whose lives and moods are significantly affected by the syndrome might also have a tougher time complying with lifestyle and treatment recommendations, all issues that need to be recognized and explored by clinicians.

Some patients do not fit the usual profile of PCOS. A special subset of patients comprises the lean PCOS patients. They represent between 10% and 50% of all PCOS patients (13) and present a challenging clinical conundrum. Despite having a normal BMI, these patients have greater insulin resistance compared to weight-matched controls (14). They also manifest various metabolic abnormalities, such as dyslipidemia (15), prothrombotic tendency, and increased proinflammatory markers. Unfortunately, their diagnosis is often delayed or missed altogether because they do not exhibit the typical obese PCOS phenotype.

Adolescents are a second atypical group. Often their diagnosis is delayed due to the assumption of the normalcy of irregular cycles after menarche and decreased severity of hirsutism. Often, oral contraceptives are initiated without a complete evaluation for PCOS. However, adolescents still have significant risks of metabolic comorbidities that could be mediated by early intervention and prevention strategies. This includes initiating weight management before severe obesity develops. Thus, it is important to complete a clinical assessment on adolescent patients that exhibits possible features of PCOS.

PATHOPHYSIOLOGY/ETIOLOGY

The exact etiology of PCOS remains unclear. Several theories have been proposed, two of which have significant supporting research. These include theories of LH dysregulation and hyperinsulinemia. As PCOS is a heterogeneous disorder with varied presentations, it is possible that both of these theories are correct but simply apply to different populations of patients. Alternatively, they could represent components of the same complex physiologic pathway. Specific research findings and potential explanations for the clinical presentation of PCOS for each theory are described.

The dysregulation of LH in PCOS patients has been reported in multiple studies and may account for many of the clinical symptoms of PCOS. Increased pulsatile gonadotropin-releasing hormone (GnRH) secretion leads to increased LH pulse frequency. The primary cause of increased GnRH is unclear; it could be an intrinsic abnormality of the pulse generator or secondary to other factors such as chronically low levels of progesterone (from anovulation) and/or hyperinsulinemia (15–18). Women with PCOS have reduced hypothalamic sensitivity to ovarian sex steroids (19) and enhanced pituitary sensitivity to GnRH that likely contribute to the increased LH secretion and pulse amplitude. The increased LH secretion relative to FSH stimulates ovarian androgen (testosterone and androstenedione) production leading to clinical hyperandrogenism. Anovulation results from insufficient selection of a dominant follicle in the setting of hyperthecosis.

Other research suggests hyperinsulinemia as the primary insult through direct and indirect effects (15). Insulin augments LH stimulation of ovarian androgen production and inhibits hepatic sex hormone–binding globulin (SHBG) production, which increases free androgen and estrogen levels. Insulin-like growth factor (IGF)-1 acts directly on the ovary to stimulate androgen production. Insulin at sufficiently high levels may cross-react with ovarian IGF receptors, enhance IGF action by upregulating IGF receptors, and inhibit IGF-binding protein (IGFBP)-1 production, leading to increased IGF-1 (17). The end result of insulin action on the ovary is the preferential production of androgens with higher free levels due to reduced SHBG. This explains how PCOS patients have hyperandrogenic symptoms despite normal androgen levels. The strong correlation of PCOS with hyperinsulinemia (see clinical presentation above) supports hyperinsulinemia as a possible central etiology.

Other physiologic effects are less well described, but may also play a role. For example, a reduction in ovarian aromatase activity has been proposed as a contributing factor to hyperandrogenism in PCOS, although this issue remains controversial (17).

MANAGEMENT

Several effective treatment strategies are available for patients with PCOS including lifestyle modifications, medications, nonmedical treatments, and surgical intervention. Given the multifaceted approach to management, a multidisciplinary team is usually needed for best results. In addition, treatment should be tailored to a patient's specific needs, with attention to reproductive goals. Several treatments are contraindicated in patients who are pursuing fertility. The optimal management of PCOS incorporates healthy changes that can be maintained for a lifetime.

Lifestyle Interventions

Lifestyle changes should be the first-line approach for any PCOS patient, particularly those with obesity. Most importantly, lifestyle intervention should address weight loss or prevention of weight gain through dietary modifications and regular exercise. A body weight reduction of 5% to 10% has been shown to exert a significant benefit on major psychological, reproductive (menstrual regulation, ovulation, fertility), and metabolic (hirsutism, insulin resistance, risk factors for diabetes and cardiovascular disease) outcomes (20). In addition, body mass index is a clear prognostic factor for infertility treatments with reduced pregnancy rates among obese PCOS patients compared to normal-weight PCOS patients. Consultation with a nutritionist who is familiar with the specific challenges of PCOS is recommended. In addition, regular exercise with a structured routine of at least 30 minutes a day can reduce cardiovascular risk associated with PCOS.

Medical Therapies

Several medical therapies effectively treat the symptoms of PCOS (Table 12.3). The choice of medications depends on the specific symptoms and their severity. Medical therapies are often optimal when combined with lifestyle interventions or nonmedical therapies.

The symptoms of menstrual irregularity and hyperandrogenism can be improved through use of the oral contraceptive pill (OCP). The maximal benefit is achieved with combined estrogen-progestin pills, since these formulations take advantage of the first-pass effect in the liver. As a result, levels of hepatic proteins, including SHBG, are significantly increased, thus reducing free circulating androgen concentrations. After initiation of OCP therapy, the regulation of the menstrual abnormality is usually immediate but improvement in hyperandrogenic symptoms may not be appreciated for four to six months. Additionally, OCPs protect the endometrium from hyperplasia by providing progesterone exposure. For all patients who have prolonged anovulation, some form of progesterone exposure is needed. For most, OCPs offer the most convenient solution. An alternative regimen is progesterone administration alone for at least 10 days per month.

Several other medical treatments for hirsutism are also available for severe symptoms or symptoms not responsive to OCPs (21) (Table 12.3). As many of these medications work via an antiandrogen mechanism, which could be teratogenic, they are often combined with the use of OCPs. Hirsutism medical therapies include spironolactone, flutamide, finasteride, ketoconazole, and eflornithine. The choice of type of treatment must consider the side-effect profile. Spironolactone (25–100 mg twice daily) acts as an androgen receptor blocker, preventing the action of androgens at the hair follicle. It is also a diuretic and should be avoided in patients with renal impairment due to increased risk of hyperkalemia. Flutamide (125–250 mg/day) is a nonsteroidal antiandrogen that is a teratogen and has been associated with hepatotoxicity rarely. Finasteride is a 5α-reductase inhibitor that prevents the formation of a potent androgen (DHT) that is the primary binding androgen at the hair follicle receptor. Finasteride is also a teratogen, but is associated with less renal or hepatic toxicity. Ketoconazole is an antifungal that inhibits steroid synthesis. Its use is limited by side effects of hypoadrenalism and hepatotoxicity. Eflornithine is an irreversible inhibitor of ornithine decarboxylase, an enzyme that is important for the growth of hair. Optimal results are achieved when combined with mechanical removal of hair (see below). Eflornithine was recently licensed by the FDA for the topical treatment facial hirsutism. The above treatments for hirsutism offer moderate results over a long term of treatment. For most of the medications, response is often not noticeable until after months of treatment. Patients pursuing fertility are poor candidates for medical therapy, given the potential for birth defect. They may choose alternative nonmedical therapies.

Table 12.3 Summary of Medical Treatments for PCOS

Medication and dose	Mechanism	Indications	Contraindications and side effects
Oral contraceptives	Suppress ovulation and ovarian androgen production	Menstrual irregularity (prevention of endometrial disease); contraception; hirsutism	Increased risk of thrombosis (low)
Spironolactone (50–100 mg twice daily)	Androgen receptor blocker and diuretic	Hirsutism	Hepatic toxicity; renal dysfunction; potential teratogen; hyperkalemia (rare); hypotension; menstrual irregularity; polyuria
Finasteride (2.5–5.0 mg daily)	5α-reductase inhibitor	Hirsutism	Teratogen (can be absorbed through skin/do not handle); potential renal or hepatic toxicity (rare)
Flutamide (250–500 mg daily)	Antiandrogen	Hirsutism	Hepatic toxicity (rare but could be severe); teratogen; yellow urine
Ketoconazole (400 mg daily)	Steroidogenesis inhibitor	Hirsutism	Adrenal insufficiency; hepatotoxicity
Eflornithine (13.9% cream twice daily)	Ornithine decarboxylase inhibitor	Hirsutism	Skin sensitivity
Clomiphene (50–150 mg x 5 days)	SERM/partial estrogen agonist at the pituitary	Ovulation induction	Multiple gestations (<10%); pituitary edema (rare) with visual changes; headache; hot flashes; mood lability
Letrozole (5–7.5 mg x 5 days)	Aromatase inhibitor	Ovulation induction	Contraindicated with hepatic disease; headaches; hot flashes
Metformin (500 mg–2000 mg daily)	Biguanide; insulin-sensitizing agent	Ovulation induction (not first-line), diabetes prevention	Contraindicated with renal or hepatic disease; lactic acidosis (higher risk if renal disease); diarrhea

Combined therapy with OCPs and antiandrogens are often utilized for higher efficacy with contraception for the teratogen risk.
Abbreviations: SERM, selective estrogen-receptor modulator; PCOS, polycystic ovary syndrome.

For patients with documented insulin resistance or glucose intolerance, insulin-sensitizing agents have been central to medical therapy. Metformin is a biguanide that acts by improving peripheral insulin sensitivity. It is currently FDA-approved for the treatment of type 2 diabetes mellitus (T2DM), but it has also been used extensively in the treatment of PCOS. Multiple studies have demonstrated an improvement in ovulation, menstrual cyclicity, and hirsutism with the initiation of metformin therapy (22). In addition, metformin improves the cardiovascular and metabolic profiles of these patients, mainly reducing their risk of T2DM (23). The recommended starting dose is 500 mg of the slow-release tablets once daily, followed by a gradual increase over weeks to months up to 2 g daily, if tolerated. Major side effects of metformin include gastrointestinal (GI) upset (diarrhea). Lactic acidosis is a significant but rare complication of metformin use and is almost exclusively encountered in patients with renal disease.

For infertility, ovulation induction with clomiphene citrate (CC) is the first-line treatment. CC is a nonsteroidal selective estrogen-receptor modulator (SERM) that acts on the pituitary to increase endogeneous production of FSH. It was the first ovulation induction agent utilized in patients with oligomenorrhea and still remains the agent of choice for anovulatory infertility. The most recent joint ESHRE/ASRM recommendations suggest CC for up to six ovulatory cycles. When administered to anovulatory PCOS patients, it results in a 60% to 80% ovulation rate and a

30% to 40% pregnancy rate. The dose of Clomid is usually started at 50 mg for five days in the follicular phase and increased up to 150 mg as needed to achieve ovulation. The main side effects associated with Clomid include multiple gestation (5% to 10%), hot flashes, and mood changes. Visual changes due to pituitary edema are rarely encountered but warrant immediate discontinuation of the medication for symptom resolution.

Metformin has also been shown to increase ovulation in PCOS patients in several small observational studies. However, it does not appear to be as effective as clomiphene for pregnancy and live birth. A randomized controlled trial by the Reproductive Medicine Network compared the efficacy of metformin and clomiphene (24); 626 PCOS patients were randomized to one of three treatment arms; CC, metformin, or CC combined with metformin. The cumulating pregnancy rates at the end of six months in the three arms were 22.5%, 7.2%, and 26.8%, respectively (Fig. 12.3; statistically significant difference). Although patients with metformin did ovulate, this did not translate to a comparable rate of live birth. Thus,

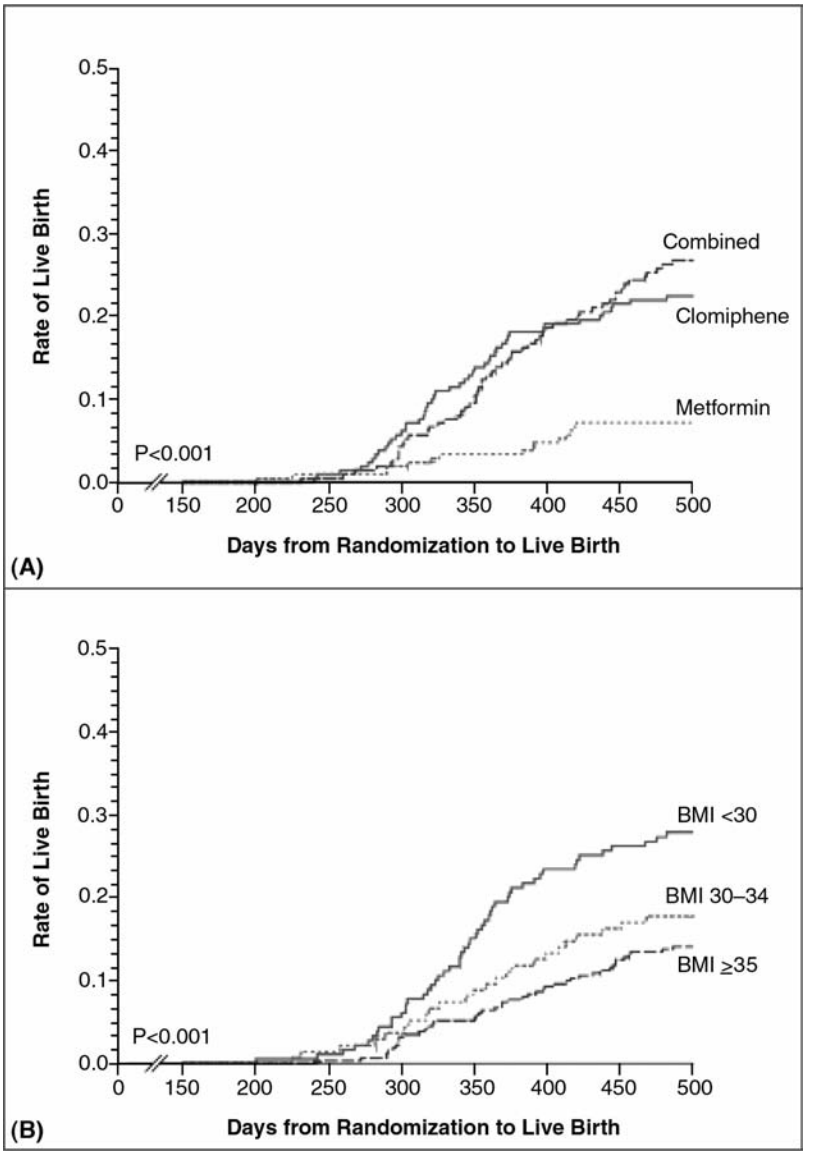

Figure 12.3 Kaplan–Meier curves for live birth rates according to study group (**A**) and BMI (**B**). Clomiphene is a superior treatment for infertility. BMI affects prognosis for all treatment groups. *Source*: From Ref. 24.

metformin as a single agent for the treatment of infertility is not recommended. A subanalysis of this study confirmed the significant role of obesity in the prognosis of patients undergoing fertility treatments. For all groups, increased body mass index was correlated with a reduced chance of a live birth (25).

Patients who fail initial treatment with Clomid either due to side effects, Clomid resistance (no ovulation at highest dose), or unsuccessful cycles can consider other treatments for infertility (26). Aromatase inhibitors (letrozole) are gaining popularity as an alternative ovulation induction agent. Treatment is associated with comparable pregnancy rates and reduction in multiple gestation risk because letrozole is associated with improved monofollicular ovulation compared to Clomid. Letrozole would also be an excellent choice for patients who have significant side effects to Clomid. Gonadotropins or in vitro fertilization offer good success rates, but can lead to an overresponse in PCOS patients and, therefore, close monitoring is essential. Patients most at risk are those with an elevated baseline anti-Mullerian hormone level and/or high antral follicle count (27). Low-dose stimulation protocols are generally employed to mediate this risk.

Nonmedical Therapies

Cosmetic procedures are frequently utilized for the treatment of hirsutism and are quite effective. These include bleaching, shaving, plucking, waxing, depilatory creams, electrolysis, light-assisted hair removal, and laser. Electrolysis and laser photothermolysis are among the most effective but also the most expensive treatments. Laser therapy is most effective in patients with darker hair and lighter skin, where selective hair follicle damage is favored. These treatments can be used in combination with medical therapies.

Surgical Interventions

The surgical treatment for ovulation induction in patients with PCOS involves multiple ovarian punctures, that is, "ovarian drilling." Prior to the advent of artificial reproductive technology (ART), ovarian wedge resection was the only treatment that was offered to the PCOS patient, with ensuing postsurgery ovulation rates reported as high as 70% to 80%. More recently, with laparoscopic advances, this procedure has progressed to laparoscopic ovarian diathermy (LOD) or laser. The main indication for surgical intervention is Clomid resistance in anovulatory PCOS patients. When compared with Clomid-metformin combination treatment, LOD resulted in comparable ovulation and pregnancy rates (28). A known complication of the procedure is adnexal adhesions. Long-term effects on ovarian function are unknown.

SUMMARY

PCOS is a complex clinical syndrome that is characterized by hyperandrogenism and ovulatory dysfunction. For accurate diagnosis, other endocrinopathies must be excluded. Presentations can vary significantly, but often include comorbidities of obesity, glucose intolerance, and other metabolic derangements. Anovulatory infertility is another hallmark of this disorder. Management is directed toward specific symptoms experienced and includes lifetime monitoring for risk factors. A multidisciplinary approach with the inclusion of lifestyle modifications is the key to optimal health outcomes for PCOS patients.

REFERENCES

1. March WA, Moore VM, Willson KJ, et al. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010; 25(2):544–551.
2. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, eds. Polycystic Ovary Syndrome. Boston: Blackwell Scientific, 1992:377–384.
3. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Fertil Steril 2004; 81(1):19–25.
4. Azziz R, Carmina E, Dewailly D, et al. Position statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006; 91(11):4237–4245.

5. Johnstone EB, Rosen MP, Neril R, et al. The polycystic ovary post-Rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. J Clin Endocrinol Metab 2010; 95(11):4965–4972.
6. Yildiz BO, Bolour S, Woods K, et al. Visually scoring hirsutism. Hum Reprod Update 2010; 16(1):51–64.
7. Ferriman and Gallwey. Clinical Assessment of Body Hair Growth in Women.. J Clin Endocrinol Metab 1961; 21:1440–1447.
8. Ehrmann DA, Barnes RB, Rosenfield RL, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999; 22(1):141–146.
9. Legro RS, Gnatuk CL, Kunselman AR, et al. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab 2005; 90(6):3236–3242.
10. Apridonidze T, Essah PA, Iuorno MJ, et al. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90(4):1929–1935.
11. Rassi A, Veras AB, dos Reis M, et al. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. Compr Psychiatry 2010; 51(6):599–602.
12. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertil Steril 2010; 93(7):2421–2423.
13. Morales AJ, Laughlin GA, Bützow T, et al. Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metab 1996; 81:2854–2864.
14. Dunaif A, Segal KR, Futterweit W, et al. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989; 38:1165–1174.
15. Ehrmann DA. Medical progress: Polycystic ovary syndrome. N Engl J Med 2005; 352:1223–1236.
16. Eagleson CA, et al. Polycystic ovarian syndrome: Evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. J. Clin. Endocrinol. Metab 2000; 85:4047–4052.
17. Salehi M, Bravo-Vera R, Sheikh A, et al.Pathogenesis of polycystic ovary syndrome: What is the role of obesity? Metab Clin Exp 2004; 53:358–376.
18. Daniels TL, Berga SL. Resistance of gonadotropin releasing hormone drive to sex steroid-induced suppression in hyperandrogenic anovulation. J Clin Endocrinol Metab 1997; 82:4179–4183.
19. Hall JE, Taylor AE, Hayes FJ, et al. Insights into hypothalamic-pituitary dysfunction in polycystic ovary syndrome. J Endocrinol Invest 1998; 21:602–611.
20. Huber-Buchholz MM, Carey DG, Normal RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999; 84:1470–1474.
21. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. Best Pract Res Clin Endocrinol Metab 2006; 20(2):221–234.
22. Tang T, Lord JM, Norman RJ, et al. Insulin-sensitising drugs for women with polycystic ovary syndrome, oligo amenorrhea and subfertility. Cochrane Database Syst Rev 2010; 20(1).
23. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346(6):393–403.
24. Legro RS, Barnhart HX, Schlaff WD, et al. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovarian syndrome. N Engl J Med 2007; 356(6):551–566.
25. Rausch ME, Legro RS, Barnhart HX, et al. Reproductive Medicine Network. Predictors of pregnancy in women with polycystic ovarian syndrome. J Clin Endocrinol Metab 2009; 94(9):3183–3184.
26. Palomba S, Falbo A, Zullo F. Management strategies for ovulation induction in women with polycystic ovary syndrome and known clomifene citrate resistance. Curr Opin Obstet Gynecol 2009; 21:465–473.
27. Nardo LG, Yates AP, Roberts SA, et al. The relationships between AMH, androgens, insulin resistance and basal ovarian follicular status in non-obese subfertile women with and without polycystic ovary syndrome. Hum Reprod 2009; 24:2917–2923.
28. Abu Hashim H, El Lakany N, Sherief L. Combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: A randomized controlled trial. J Obstet Gynaecol Res 2010 [Epub ahead of print].

13 Fertility preservation for cancer patients

David A Ryley

In 2009, there were 713,220 new cases of cancer diagnosed in the United States among females, and from 2003 to 2005, the probability of a cancer diagnosis among premenopausal women was 11% (1). Improved cancer surveillance and treatment regimens have resulted in decreased mortality rates among this cohort, allowing these women to focus on survival and quality of life, including preservation of fertility. From 1991 to 2005, overall cancer death rates decreased by 11.4%, with decreases in breast cancer accounting for 37% of the total decrease. Malignancies affecting younger women, such as breast cancer, cervical cancer, lymphoma, and leukemia have increased survival rates of greater than 80%.

In the United States, cancer is the second most common cause of death among children between the ages of 1 and 14 years (2.3/100,000), surpassed only by accidents (1). The success of oncologic therapies is even more pronounced among cancers affecting these patients, including leukemia, cancers of the brain and nervous system, soft tissue sarcomas, renal tumors, and non-Hodgkin's lymphoma. The five-year relative survival rate among children for all cancer sites combined improved from 58% for patients diagnosed in 1975 to 1977 to 80% from 1996 to 2004 (1). As of 2010, it is projected that 1/250 adults are long-term survivors of a childhood malignancy (2).

EFFECTS OF CHEMOTHERAPY AND RADIATION ON FERTILITY

Many treatments that have improved survival among both adults and children diagnosed with cancer are gonadotoxic, especially those that employ high doses of alkylating agents and radiation therapy directed near or toward the pelvis. The impact on the ovarian reserve is related to the accelerated depletion of the primordial germ cell pool resulting from these therapies.

Oogenesis is a process that begins in utero, approximately three weeks after conception, when the primordial germ cells derived from the endodermal yolk sac initiate their migration to the developing ovaries. These cells then undergo an inexorable differentiation to become primary oocytes which, at the time of birth, are arrested in the prophase of the first meiotic division. At this time, there is no further differentiation of the germ cells, but a continuous apoptotic loss that depletes the supply from 1 to 2 million at birth to 300,000 to 500,000 at the time of puberty. Under the proper hormonal conditions, an ovum completes its first meiotic division in response to the maturation of the hypothalamic-pituitary-ovarian axis and the LH surge that causes the release of the oocyte on a monthly basis. Through ovulation and continued atresia of the nondominant follicles, the ovarian reserve is eventually depleted with an exponential loss of oocytes occurring at the age of 37 years up until the time of the menopause (3).

Alkylating agents (such as cyclophosphamide, ifosfamide, nitrosoureas, chlorambucil, melphalan, and busulfan), which are not cell-cycle specific, confer their deleterious effect on the vast supply of primordial germ cells and carry the highest risk of ovarian failure (Table 13.1). Antimetabolites (such as methotrexate, bleomycin, 5-fluorouracil, actinomycin-D, mercaptopurine, vincristine) impact the cells (granulosa and oocyte) of the metabolically active ovarian follicles and are considered to be low risk for gonadal dysfunction, while cisplatin appears to carry intermediate risk between the antimetabolites and alkylating agents (4).

Women over the age of 40 years have a 90% chance of amenorrhea subsequent to multiagent chemotherapy, whereas the potential for premature ovarian failure in younger patients varies between 20% and 90% (5). All patients exposed to chemotherapy will have a diminished ovarian reserve and, therefore, potential infertility with a significant predisposition for developing premature ovarian failure. Chemotherapy treatments may, in fact, be the leading cause of premature ovarian senescence, since 2% of the female population between the ages of 1 to 39 will be diagnosed with cancer, and half of these patients will require treatment with chemotherapy (1).

Table 13.1 Ovarian Toxicity of Various Chemotherapeutic Agents

Chemotherapeutic agent	Ovarian toxicity
Alkylating agents	
Cyclophosphamide, ifosfamide, nitrosoureas, chlorambucil, melphalan, and busulfan	High
Cisplatin	Intermediate
Antimetabolites	
Methotrexate, bleomycin, 5-fluorouracil, actinomycin-D, mercaptopurine, vincristine	Low

The tolerance of the ovary and uterus to radiation exposure is dependent on several factors including the age of the patient, the volume of irradiated tissue, the total dose of radiation, the risk of scatter, and the fractionation schedule. When applied conventionally, radiation doses of 24 Gy will result in ovarian failure. If the pelvis is included in the radiation field of an adult patient, the dose will typically exceed this level (6). Doses of radiation between 14 and 30 Gy result in uterine dysfunction, increasing the risk of obstetric complications in future pregnancies (7).

The use of more precise radiation treatments has afforded oncologists the opportunity to decrease the exposure of the ovaries to the field of radiation. Three-dimensional computerized analysis of the dose of radiation received by the ovaries can allow more precise treatment and mitigate the gonadotoxic potential. For a given dose of radiotherapy at a known chronological age, oncologists can now predict the size of the surviving fraction of oocytes, and, therefore, the age at which ovarian failure can be expected for a patient (8). These projections will serve the patient well as she and her physicians contemplate the timing and utility of fertility preservation strategies.

The greatest risk for developing premature ovarian failure occurs in the setting of the intensive multiagent chemotherapy and total body irradiation that is required for both adults and children who undergo bone marrow stem cell transplantation (BMSCT) for treatment of their malignancies. The doses required cause immediate ovarian failure in nearly all cases (5). Chemotherapy treatments, most including cyclophosphamide, as well as BMSCT are also utilized in the treatment of benign and chronic diseases such as sickle-cell anemia, thalassemia, aplastic anemia, lupus, and autoimmune thrombocytopenia (9,10). Additional benign indications for fertility preservation technologies include recurrent ovarian endometriosis, ovarian cysts, and the need for prophylactic oophorectomy in women affected by BRCA-1/2.

FERTILITY PRESERVATION GUIDELINES

In March 2005, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) published their guidelines for the preservation of fertility in cancer patients (11). Faced with the prospect of gonadotoxic cancer therapies, individuals are now able to preserve their fertility through the use of embryo cryopreservation from in vitro fertilization (IVF), and potentially with emerging techniques such as oocyte and ovarian tissue cryopreservation. The committee indicated that the only established methods of fertility preservation are sperm cryopreservation in males for use with intracytoplasmic sperm injection (ICSI) during IVF, and embryo cryopreservation (11). Oocyte and ovarian tissue cryopreservation are deemed experimental procedures and, as such, should only be offered with Investigational Review Board (IRB) oversight in a research setting. The authors express that concerns about the welfare of the potential offspring *should not* be cause for denying cancer patients assistance in reproducing. When raised in a loving and nurturing environment, children should be given the opportunity to thrive, despite the misfortune of an early death of one parent.

These recommendations parallel those published by the American Society of Clinical Oncology (ASCO) in 2006 (12). The authors recommended that oncologists should consider the options for fertility preservation expediently, so as to facilitate discussions with reproductive specialists and advocacy groups that support these treatments. Established methods, in addition to embryo and sperm cryopreservation, include gonadal shielding and ovarian transposition in cases involving exposure of the pelvis to radiation therapies. Encouragingly, the ASCO guidelines confirm that there appears to be no increased risk of disease recurrence

associated with use of the established treatments, even in tumors that might be hormonally sensitive, that is, breast cancer. Also, there is no evidence of an increased risk of congenital abnormalities in the progeny of patients who have attempted to preserve their fertility, except in those cases that involve hereditary genetic syndromes (12).

NONSURGICAL FERTILITY PRESERVATION TECHNIQUES

Embryo Cryopreservation

Embryo cryopreservation, routinely performed in patients undergoing IVF, affords the patient an optimal chance to preserve her fertility, with pregnancy rates of 20% to 50% per transfer of two to three thawed embryos, depending on the age of the patient at the time of her oocyte retrieval (13). However, this approach requires a source of sperm, a problematic option for patients without a partner. Additionally, the treatment could not be offered to prepubertal patients who have an undeveloped reproductive endocrine axis, or to adolescents who can neither provide consent nor use donor sperm. Concerns related to the oncogenic potential of supraphysiologic levels of gonadotropins and estradiol resulting from IVF on the course, prognosis, and treatment of estrogen-dependant neoplasms may decrease the utility of this treatment for certain patients (14). Protocols for controlled ovarian hyperstimulation (COH) that include agents such as letrozole (aromatase inhibitor) and tamoxifen (selective estrogen receptor modulator) in conjunction with gonadotropins appear to yield high-quality embryos and counteract the potential impact of high estradiol levels (15). When implemented in close collaboration with the patient's oncology team, these protocols can be completed for breast cancer patients during the four to six week interval that typically occurs between the patient's surgery and the initiation of chemotherapy. However, such a delay in treatment renders this technique impractical for other cancers. Additional concerns pertain to the moral dilemma that may result from the creation and disposition of human embryos produced solely for future use (16).

Oocyte Cryopreservation

Similar to embryo cryopreservation, oocyte cryopreservation results in elevated serum estradiol levels and requires a mature reproductive axis, the use of gonadotropins for COH, and delays in the timing of chemotherapy treatment. However, there is no need for a male partner or donor sperm, and issues related to the creation of surplus embryos are avoided. Oocyte freezing was heretofore considered an elusive and challenging technique due to the unique properties of the human oocyte, particularly with its large water content and the fragility of the meiotic spindle (17). Inefficiencies in the success of this technology were the result of increased ice crystal formation and hardening of the zona pellucida caused by the premature release of cortical granules, which, in turn, prevented the fertilization of the thawed oocyte (18). Recently, with the use of cryoprotectants that limit osmolarity changes, rapid freezing techniques known as vitrification, and fertilization with ICSI, multiple clinics have reported increased success after the uterine transfer of embryos resulting from the fertilization of thawed oocytes (18,19). At our center, a recent study involved the cryopreservation of 140 metaphase II (MII) oocytes retrieved from eight anonymous donors. Of these, 118 (84.3%) survived the freeze-thaw process, and ICSI with partner sperm resulted in a fertilization rate of 79.7%; 92 (97.9%) of the resulting embryos attained the cleavage stage, and 27/62 (43.5%) of the biopsied embryos were determined to be euploid by preimplantation genetic analysis. The transfer of 12 of these blastocysts into six patients yielded a clinical pregnancy rate of 66.7% (4/6 patients) and four term deliveries (three singletons and one set of twins) (20). In a study of subjects undergoing the transfer of embryos derived from autologous and donor frozen/thawed oocytes, the pregnancy rates were similar to age-matched controls undergoing conventional IVF (21).

In Vitro Maturation

As an alternative, in vitro maturation (IVM) of oocytes retrieved from unstimulated ovaries is an option for fertility preservation for young women who would neither require the participation of a male partner nor delays in cancer treatments. The IVM and freezing of these oocytes, similar to oocyte and ovarian tissue cryopreservation, is considered an

experimental technique that has been typically used for the treatment of infertility in women with the polycystic ovarian syndrome (PCOS). This technology has been used in conjunction with ovarian tissue cryopreservation, allowing the aspiration of antral follicles prior to the cryobanking of ovarian tissue that has been surgically retrieved (22). Live births have been reported from this procedure; its application is limited to specialized centers. Future research may focus on the retrieval of the oocytes following the thawing of cryopreserved ovarian tissue.

SURGICAL FERTILITY PRESERVATION TECHNIQUES

Gynecologic Malignancies

Surgical techniques for the preservation of fertility among patients with early-stage cervical cancer allow preservation of the uterus and ovaries, and include *radical trachelectomy* with or without lymph node dissection (23). Women diagnosed with microinvasive cervical cancer (stage 1A1), without lymphovascular space involvement, are candidates for a cone biopsy (24). Antepartum management for these women requires close observation for cervical incompetence, and the potential need for prophylactic cerclage placement.

Oophoropexy and ovarian transposition, which limit gonadotoxicity induced by radiation exposure, are established surgical techniques offered to women who are undergoing radiation therapy for cancers involving the pelvis, such as cervical cancer, colon cancer, or metastatic Hodgkin's lymphoma (25,26). As mentioned above, uterine exposure to pelvic/abdominal radiation may require the use of gestational carriers in future pregnancies to eliminate the risk of obstetric complications related to these treatments.

Women with ovarian cancer, such as those with early-stage germ-cell tumors, or select cases of stage I epithelial ovarian cancers, are candidates for fertility preservation procedures that involve unilateral salpingo-oophorectomy of the diseased ovary in conjunction with uterine preservation (27,28).

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is an experimental option for women who, due to the need for immediate chemotherapy or radiation treatments, are not candidates for more established techniques such as embryo cryopreservation from IVF. Typically, women diagnosed with blood-borne malignancies or those who face BMSCT for either primary or recurrent/metastatic disease (as well as certain benign conditions) would benefit from ovarian tissue cryopreservation. Prepubertal girls, who have yet to develop a mature hypothalamic-pituitary-ovarian axis, would also qualify for this novel procedure. Although promising for these patients, there are few live births to date that have resulted from the cryopreservation and orthotopic or heterotopic reimplantation of thawed ovarian tissue (29).

Concerns with the transplantation of cryopreserved-thawed ovarian tissue focus on the risk of disease recurrence emanating from the exposure of cancer survivors to diseased tissue that harbors malignant cells. Fortunately, the ovary is not considered to be a typical sanctuary for blood-borne malignancies (30,31). In an Israeli study in 2008, 58 patients with hematologic malignancies, including non-Hodgkin's lymphoma, acute leukemia, myelodysplastic syndrome, chronic myeloid leukemia (CML), and Hodgkin's lymphoma, were evaluated for storage of ovarian tissue for fertility preservation. Two of the subjects were excluded from the study due to preoperative imaging confirming the presence of macroscopic ovarian metastases. Of the remaining patients, post-thawing tissue analysis confirmed the presence of minimal residual disease in only one patient, retrieved from a patient with CML (32).

CONCLUSION

Cancer treatments, despite their gonadotoxicty, have allowed survivors to focus on an enhanced quality of life, including the ability to have a biologic child. Both established and experimental therapies can now be utilized to allow these women to overcome the infertility that may result from their chemotherapy and radiation therapies. Continued research into the surgical and nonsurgical approaches to fertility preservation is warranted.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009; 59(4):225–249.
2. Bleyer WA. The impact of childhood cancer on the United States and the world. CA Cancer J Clin 1990; 40(6):355–367.
3. Speroff L, Fritz M. Clinical Gynecologic Endocrinology and Infertility. 7th ed. Lippincott Williams and Wilkins, Philadelphia; 2005.
4. Bokemeyer C, Schmoll HJ, van Rhee J, et al. Long-term gonadal toxicity after therapy for Hodgkin's and non-Hodgkin's lymphoma. Ann Hematol 1994; 68(3):105–110.
5. Lobo RA. Potential options for preservation of fertility in women. N Engl J Med 2005; 353(1):64–73.
6. Grigsby PW, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. Int J Radiat Oncol Biol Phys 1995; 31(5):1281–1299.
7. Crictchley H, Hamish B. Safety of pregnancy during and after cancer treatment. J Natl Cancer Inst Monogr 2005; 34:64.
8. Wallace WH, Thomson AB, Saran F, et al. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005; 62(3):738–744.
9. Mattle V, Behringer K, Engert A, et al. Female fertility after cytotoxic therapy—protection of ovarian function during chemotherapy of malignant and non-malignant diseases. Eur J Haematol Suppl 2005; (66):77–82.
10. Slavin S, Nagler A, Aker M, et al. Non-myeloablative stem cell transplantation and donor lymphocyte infusion for the treatment of cancer and life-threatening non-malignant disorders. Rev Clin Exp Hematol 2001; 5(2):135–146.
11. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005; 83(6):1622–1628.
12. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006; 24(18):2917–2931.
13. Centers for Disease Control and Prevention. 2008 Assisted reproductive technology success rates: national summary and fertility clinic reports. Available at: http://www.sart.org.
14. Yue W, Santen RJ, Wang JP, et al. Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis. J Steroid Biochem Mol Biol 2003; 86(3–5):477–486.
15. Oktay K, Hourvitz A, Sahin G, et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab 2006; 91(10):3885–3890.
16. Porcu E, Venturoli S. Progress with oocyte cryopreservation. Curr Opin Obstet Gynecol 2006; 18(3):273–279.
17. Chen SU, Lien YR, Chao KH, et al. Effects of cryopreservation on meiotic spindles of oocytes and its dynamics after thawing: clinical implications in oocyte freezing—a review article. Mol Cell Endocrinol 2003; 202(1–2):101–107.
18. Vincent C, Pickering SJ, Johnson MH. The hardening effect of dimethylsulphoxide on the mouse zona pellucida requires the presence of an oocyte and is associated with a reduction in the number of cortical granules present. J Reprod Fertil 1990; 89(1):253–259.
19. Fabbri R, Porcu E, Marsella T, et al. Human oocyte cryopreservation: new perspectives regarding oocyte survival. Hum Reprod 2001; 16(3):411–416.
20. Kinzer D, Alper M, Barrett B. Abstract P-045. The American Society for Reproductive Medicine Annual Meeting, October 2008; San Francisco, CA.
21. Grifo JA, Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. Fertil Steril 2010; 93(2):391–396.
22. Huang JY, Tulandi T, Holzer H, et al. Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy of fertility preservation. Fertil Steril 2008; 89(3):567–572.
23. Plante M, Renaud MC, Francois H, et al. Vaginal radical trachelectomy: an oncologically safe fertility-preserving surgery. An updated series of 72 cases and review of the literature. Gynecol Oncol 2004; 94(3):614–623.
24. Bisseling KC, Bekkers RL, Rome RM, et al. Treatment of microinvasive adenocarcinoma of the uterine cervix: a retrospective study and review of the literature. Gynecol Oncol 2007; 107(3):424–430.
25. Scott SM, Schlaff W. Laparoscopic medial oophoropexy prior to radiation therapy in an adolescent with Hodgkin's disease. J Pediatr Adolesc Gynecol 2005; 18(5):355–357.
26. Morice P, Juncker L, Rey A, et al. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. Fertil Steril 2000; 74(4):743–748.
27. Simon B, Lee SJ, Partridge AH, et al. Preserving fertility after cancer. CA Cancer J Clin 2005; 55(4):211–228; quiz 263–264.

28. Schilder JM, Thompson AM, DePriest PD, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol 2002; 87(1):1–7.
29. Oktay K, Oktem O. Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience. Fertil Steril 2010; 93(3):762–768.
30. Khan MA, Dahill SW, Stewart KS. Primary Hodgkin's disease of the ovary. Case report. Br J Obstet Gynaecol 1986; 93(12):1300–1301.
31. Osborne BM, Robboy SJ. Lymphomas or leukemia presenting as ovarian tumors. An analysis of 42 cases. Cancer 1983; 52(10):1933–1943.
32. Meirow D, Hardan I, Dor J, et al. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. Hum Reprod 2008; 23(5):1007–1013.

RECOMMENDED READING

Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005; 83(6):1622–1628.
Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006; 24(18):2917–2931.
Lobo RA. Potential options for preservation of fertility in women. N Engl J Med 2005; 353(1):64–73.

14 Recurrent pregnancy loss

Benjamin Lannon and Alison E Zimon

The evaluation and management of couples with recurrent pregnancy loss (RPL) can often be challenging for both the clinician and patient. For the patient, the devastation caused by a single pregnancy loss, let alone repeated losses, is emotionally straining and further burdensome due to uncertain causality and prognosis. The clinician is faced with addressing the psychosocial needs of the patient while embarking on a complex and sometimes ambiguous series of tests and treatment options that may not guarantee the desired outcome of a healthy live birth. Caring for the RPL patient requires responsiveness to the evolving diagnostic and treatment algorithms for RPL, while focusing on the individual needs and therapy goals of the patient.

DEFINING RECURRENT PREGNANCY LOSS

Traditionally, RPL has been defined as three or more losses. The Practice Committee of the American Society of Reproductive Medicine (ASRM) defines RPL as "... a disease distinct from infertility, defined by two or more failed pregnancies. When the cause is unknown, each pregnancy loss merits careful review to determine whether specific evaluation may be appropriate. After three or more losses, a thorough evaluation is warranted" (1). The ASRM definition is restricted to clinically recognized pregnancy losses, with pregnancy confirmed by ultrasonography or histopathologic examination. In efforts to minimize the unnecessary hardship to patients who may suffer otherwise preventable pregnancy loss, most clinicians favor diagnosing an RPL after two consecutive losses, despite recognition of the effort and cost associated with a full RPL diagnostic evaluation. It is important to note that many of the potential etiologies of RPL are not absolute, so the occurrence of interval live births does not preclude a diagnosis of RPL (2). Certainly, each case of RPL should be considered individually and recommendations be based on the needs of the specific couple including their history of loss, prior live births, or other obstetric complications, rather than pure focus on the number of miscarriages (3).

INCIDENCE

In young women, 15% to 20% of clinically recognized pregnancies and upward of 50% of all pregnancies undergo spontaneous loss. These figures increase substantially with maternal age to as high as 40% and 85% respectively in women 40 years and older. The chance of having two consecutive losses is 5% with 1% of couples experiencing three consecutive miscarriages (1).

ETIOLOGY

A number of etiologies have been proposed for RPL and they may present alone or in combination (Fig. 14.1). When counseling patients with RPL, it is helpful to present the potential etiologies in broad terms including anatomic factors, genetic variations, endocrinopathies, thrombophilias, autoimmune phenomena, and infectious etiologies. Despite these various potential causes, the majority of cases of RPL, around 50%, remain unexplained (4), a feature of this condition that is met with further frustration and helplessness by patients. In addition, due to the nonspecific nature of many of these etiologies, there is potential to attribute the cause of RPL to an incidental finding.

An important consideration in the evaluation of RPL is the age of the patient, as the rate of spontaneous miscarriage increases with maternal age. This is not included in the formal definition of RPL and other causes of RPL can occur at any age. However, the clinician must assess the role of declining oocyte quality and age-related spontaneous aneuploidy rates when beginning an assessment (2). Another consideration is the timing of the miscarriage. Sometimes, due to a specific etiology, RPL tends to occur at the same gestational age. Factors

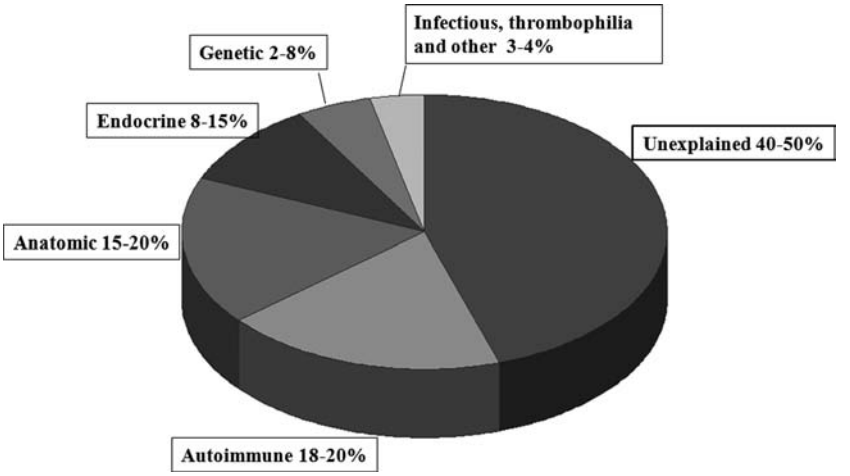

Figure 14.1 Causes of recurrent pregnancy loss.

associated with embryonic loss, <10 weeks' gestation, are different from those presenting with late RPL typically between 10 and 16 weeks' gestation (5). Likewise, there are obstetric factors, such as cervical insufficiency, that may contribute to late second-trimester loss or extreme preterm delivery that are not included in this topic.

Anatomic Factors

Anatomic factors contributing to RPL are divided into congenital and acquired factors and together account for 15% to 25% of RPL. Congenital anomalies, including septate, bicornuate, unicornuate, and didelphic uteri, are found more commonly in women with RPL than the general population. Septate uterus is the most prevalent anomaly and also is the anomaly most tightly linked to reproductive failure, with an associated pregnancy loss rate as high as 79% (6). An association between arcuate uterus and RPL is uncertain (7). However, the specific contribution of these findings to RPL is difficult to quantify due to the varying diagnostic and management techniques reported in the literature. The pathophysiology is thought to be primarily a vascular phenomenon where there is reduced perfusion of the uterine septum and abnormal development of the overlying endometrium (5,8).

Acquired uterine factors such as fibroids, polyps, and Asherman's syndrome may also contribute to RPL. These factors may have some impact on embryonic implantation or uterine receptivity. The contribution of these pathologies to abnormal implantation, placentation, and pregnancy growth are speculative but are likely similarly related to aberrant vascularization and insufficient endometrial support of the pregnancy combined with alterations in the intrauterine immunological milieu favoring inflammation rather than growth (6).

Genetic Factors

In sporadic loss, chromosomal abnormalities account for at least 50% of clinically diagnosed spontaneous abortions and perhaps upward of 60% to 75% of all pregnancy losses (9). In RPL, 25% to 51% of fetal losses are demonstrated to be aneuploid (3).

In sporadic pregnancy loss due to aneuploidy, age is certainly the major determining factor with the chance of loss increasing directly with age from 15% to 20% prevalence in women less than 35 years of age to 40% in women over 40 years. This is attributable to the accumulated risk of acquired meiotic segregation errors that lead to oocyte and embryonic aneuploidy. Interestingly, the correlation of age-related aneuploidy is similar in the sporadic and RPL populations, suggesting that some cases of RPL, particularly in women over the age of 35 years, are due to probability alone (9). Whether there are age independent predispositions to recurrent aneuploidy is unclear.

Parental structural chromosome abnormalities are observed in 2.5% to 8% of RPL (3,10,11). Translocations account for the majority of these cases and include balanced reciprocal translocations, in which two different segments of parental autosomes are exchanged, and balanced Robertsonian translocations, in which the long arms of two acrocentric chromosomes (chromosomes 13, 14, 15, 21, 22) join to form a single new chromosome. Chromosome inversions and other parental karyotypic abnormalities are seen as well. In some series, translocations are more commonly found in the female partner of a couple with RPL and are more likely to result in loss than male-derived translocations. Couples with a translocation may present with a history of prior live birth, RPL at an early age, or a family history of RPL (2). Segregation genetics would suggest predictable rates of unbalanced, balanced, and normal chromosomes in conceptuses. Yet in reality, the distribution is skewed and a relatively lower rate of balanced and normal pregnancies are observed than would be expected resulting in a higher embryo and pregnancy loss rate (9). Nevertheless, both miscarriages and normal pregnancies are possible outcomes in cases of parental balanced translocations, and a history of recurrent losses interspersed with normal full-term pregnancies should instigate parental chromosome testing.

Endocrinopathies

The primary endocrinopathies associated with RPL are thyroid dysfunction, hyperprolactinemia, diabetes mellitus, and the polycystic ovarian syndrome.

A euthyroid state is critical for optimal function in reproduction and pregnancy and poorly controlled thyroid disease has been associated with poor pregnancy outcome and RPL. The prevalence of abnormal thyroid function may be 3% to 7% in the RPL population (3). Further, even a subtle hypofunction of the thyroid, as in subclinical hypothyroidism, or euthyroidism in the presence of thyroid autoimmunity (the presence of thyroid peroxidase and thyroglobulin antibodies) may be associated with failed placentation and RPL (12). While not confirmed, the etiology may relate to the increased demands of thyroid hormone in pregnancy, the resulting impact on placental growth, and a potentially detrimental effect of thyroid antibodies on the placenta (13).

A connection between glycemic control and insulin resistance on maintaining an ongoing healthy pregnancy has been established. Well-controlled diabetes mellitus does not seem to increase the risk of pregnancy loss. However, poor control is associated with RPL, and this may be related to the impact of hyperglycemia toward worsening underlying vascular disease, or impact of insulin resistance on fibrinolysis during placentation (2). The prevalence of previously undiagnosed frank diabetes is expected to be low (<1%) in the RPL population (3). Higher rates of pregnancy loss in PCO lends further evidence that insulin resistance, alone or combined with hyperandrogenism, may have a negative impact on placental growth and maintenance of pregnancy, and among patients with RPL the prevalence of PCO is as high as 36% to 56% (7).

Abnormal prolactin levels can be associated with RPL potentially relating to an association with autoimmunity as in lupus or antiphospholipid syndrome or alternatively as a marker of hypothalamic-pituitary dysfunction in the setting of neuroendocrine stress (7).

The impact of deficient production of progesterone in the luteal phase has been hypothesized as a cause of RPL, though substantial data to prove a causality between progesterone deficiency or adequacy and pregnancy outcome has not been established (2,7,14).

Inherited Thrombophilias

Thrombophilia is defined as any disorder associated with an increased risk of thrombosis and venothromboembolism (VTE), and a number of inherited thrombophilias have been connected with RPL and other obstetric complications (15). Specific inherited thrombophilias linked to adverse obstetric outcomes and pregnancy loss include Factor V Leiden mutation, prothrombin gene mutation, antithrombin III deficiency, protein C deficiency, and protein S deficiency. While early data suggested that methylene tetrahydrofolate reductase mutations and hyperhomocysteinemia caused VTE, more recent data has not validated this causality. Perhaps the most controversial of the etiologies, the association, causality, and treatment of inherited thrombophilias in patients with RPL is a source of debate in the field. Some studies

demonstrate no increased prevalence of heritable thrombophilias in the RPL population (3). The thrombosis of uteroplacental vessels underlies the theoretical pathobiology of these conditions and they are typically associated with late RPL, and the role of thrombophilias in early pregnancy and embryonic loss (<10 weeks) is unclear (16). Likewise, the degree of risk for RPL and efficacy of treatment have been debated in the literature and in practice (17).

Autoimmune Phenomena

The antiphospholipid antibodies are the most significant autoimmune phenomena associated with RPL occurring in 18% to 20% of cases (3,10,18). Antiphospholipid antibodies have been associated with both recurrent embryonic and fetal (>10 week) loss. In addition they have been connected with other obstetric complications such as preeclampsia and growth restriction, as well as venous thromboembolism (19). Specific diagnostic criteria for the antiphospholipid antibody syndrome are listed below as well as indications for testing. There is likely an overlap between patients with isolated positive antibodies and unrelated sporadic miscarriage and therefore testing should be done with an appropriate history (17). Likewise, given the potential for additional obstetric and maternal complications, treatment guidelines should be followed. The role of other antibody and rheumatologic testing such as phosphatidyl inositol, ANA, and specific lymphocyte testing is uncertain.

Infectious Etiologies

On the basis of associations with sporadic miscarriage, identification and treatment of certain microorganisms have been proposed in the evaluation of RPL. However, no studies have clearly identified infectious agents as a cause for RPL and therefore screening for *Chlamydia*, *Mycoplasma*, and *Ureaplasma* species is not recommended (2).

Lifestyle and Exposures

Lifestyle stress has been frequently implicated anecdotally and scientifically as an etiology for pregnancy loss and RPL. It is believed that stress-induced increases of adrenocoticosteroids or stress-induced decreased immunity may negatively impact the ability to maintain a pregnancy. Dietary factors including high caffeine intake of the equivalent of over three cups of coffee a day or low antioxidant serum levels are associated with RPL (20). Tobacco smoking and other toxic environmental exposures have also been associated with RPL. While the data is not conclusive, a possible link between these lifestyle factors cannot be completely excluded (21).

Other

Several additional rare or less well-defined conditions may be associated with spontaneous miscarriage and possibly RPL. These include celiac disease, obesity, diminished ovarian reserve, and teratospermia.

EVALUATION AND HISTORY

For patients and clinicians alike, the uncertainty of the etiology and inability to predict recurrence of RPL, creates a strong incentive to identify a specific cause. While an extensive battery of testing could be performed, likely the best approach is to limit diagnostics to identify etiologies where causality and therapy options have been established by evidence-based research (Table 14.1). The initial approach includes a thorough medical history and physical exam with attention to details of timing and outcomes of prior pregnancies and miscarriages, presence of uterine and pelvic factors, and evidence of associated medical conditions.

Personal and Familial History

The personal history questionnaire should include symptoms and diagnoses related to endocrinopathies, autoimmune disorders, coagulopathies, obesity, and infections, lifestyle, and environmental exposures. The reproductive history should include past uterine instrumentation, pelvic infection, total number of pregnancies, and outcomes. Pregnancy loss history should specify sequential or sporadic timing of pregnancy, the gestational age at diagnosis, whether fetal cardiac activity was documented, management, comorbidities, and

Table 14.1 Diagnostic Testing for Recurrent Pregnancy Loss

Uterine cavity defects and Mullerian anomalies	Hysterosalpingogram Saline-infused sonography 3D ultrasound or MRI Diagnostic hysteroscopy
Chromosomal abnormalities	Fetal tissue chromosome analysis by karyotype, FISH, or CGH Parental chromosome analysis by karyotype, FISH, or CGH
Endocrinopathies	TSH, FT4, antithyroid peroxidase antibodies, antithyroglobulin antibodies Fasting glucose, hemoglobin A1C% Prolactin Cycle day-3 FSH and estradiol
Antiphospholipid syndrome	Lupus anticoagulant, anticardiolipin IgG and IgM antibodies, anti-β2 glycoprotein-1 antibodies
Inherited thrombophilia	Factor V Leiden gene mutation, prothrombin G20210A gene mutation, protein C and protein S functional assay, antithrombin III levels
Infectious	Genital cultures (symptom based)
Other	Screening for exposures, celiac disease, teratospermia, obesity

Abbreviations: FISH, flourescent in situ hybridization; CGH, comparative genomic hybridization; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

fetal chromosome data if available. Familial history should include a thorough screening for RPL, stillbirth, or other fetal loss, as well as mental retardation, endocrinopathies, autoimmune disorders, coagulopathies, and obesity.

Physical Examination

Specific focus on the physical exam should be placed on identifying signs of thyroid disease, diabetes, lupus, rheumatoid arthritis, other autoimmune disorders, and pelvic anatomy.

DIAGNOSTIC TESTING

It is recommended to initiate a diagnostic evaluation of RPL after two consecutive recurrent pregnancy losses. This approach is favored over waiting for the classic definition of three consecutive losses in part to minimize further distress to a patient should a treatable etiology be identified. Further, the probability of identifying a pathophysiological factor through testing is similar (40%) in patients with two and with three consecutive losses (3,17).

Uterine Examination

A hysterosalpingogram (HSG) is the preferred single uterine cavity study. This allows accurate diagnosis of uterine anomalies, as well as detects intracavitary masses or lesions with a positive predictive value of upward of 85%. If HSG findings are not definitive, or if more specific testing is desired, a saline-infused sonography (SIS) is recommended to detect intracavitary lesions with a positive predictive value of 95%. If definitive diagnosis is desired or intracavitary lesions are suspected based on prior radiological studies, hysteroscopy in the office or operative setting should be performed. If a congenital uterine anomaly is suspected based on HSG or SIS, a 3D ultrasound or pelvic MRI can be performed (Fig. 14.2).

Genetic Testing

A chromosomal analysis on both partners is recommended to asses for parental potential structural chromosomal abnormalities. In the patient with RPL, analysis of fetal chromosomes will prove extremely helpful, particularly as evidence of sporadic aneuploidy may be definitively diagnostic and obviate additional testing. The routine and traditional method of chromosome analysis is a metaphase spread karyotype on cultured parental blood lymphocytes or cultured chorionic villi cells. An additional option is employing newer comparative genomic hybridization (CGH) technologies which, in the cases of aneuploidy, identify the paternal or the maternal line as the source for the acquired or inherited defect.

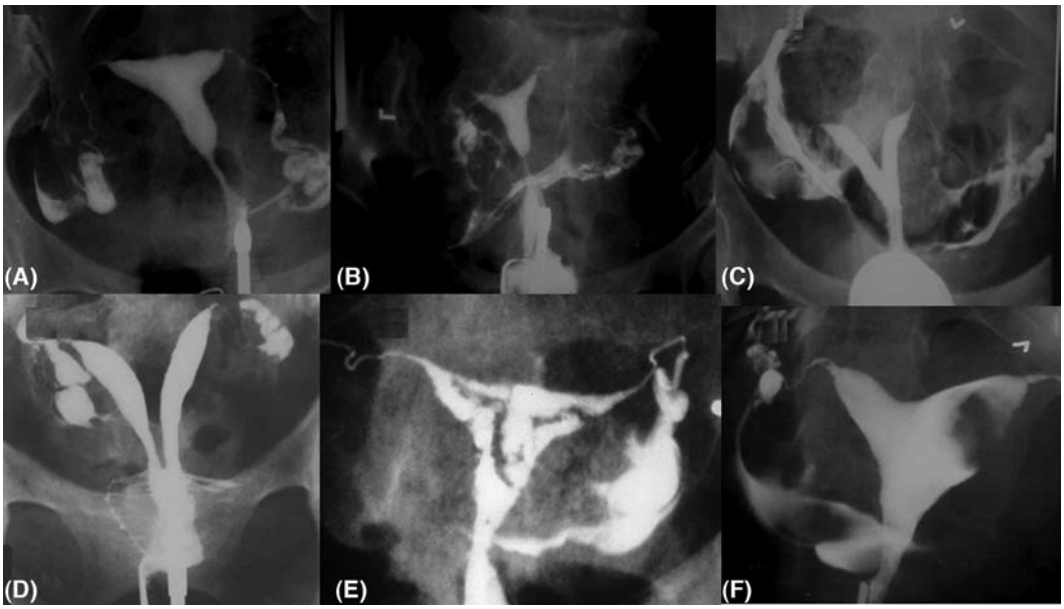

Figure 14.2 Hysterosalpingogram (HSG) images—the HSG is the preferred test to evaluate the uterine cavity in cases of RPL. The HSG images are as follows: (**A**) Normal uterine cavity; (**B**) arcuate cavity—note the slight depression impinging on the superior aspect of the cavity; this has no clinical significance; (**C**) uterine septum coming half way down the cavity; (**D**) a complete uterine septum; to differentiate a uterine septum versus bicornuate uterus, it is recommended to do a 3D ultrasound or MRI; (**E**) Asherman's syndrome; and (**F**) intracavity uterine fibroid.

Endocrine Testing

The panel of endocrine testing to screen for potential endocrinopathies associated with RPL includes tests to assess for underlying thyroid disease, hyperprolactinemia, diabetes, and diminished ovarian reserve.

Specifically, this serological testing panel includes thyroid-stimulating hormone (TSH), with or without free thyroxine (FT4), antithyroid peroxidase antibodies and antithyroglobulin antibodies, prolactin (PRL), fasting glucose or HgbA1C, and cycle day-3 follicle-stimulating hormone (FSH) and estradiol.

Diagnostic Testing for Antiphospholipid Syndrome

To fulfill the laboratory testing criteria for antiphospholipid syndrome (APS), it is required to demonstrate positive serum antiphospholipids at significant levels on two or more occasions and at least 12 weeks apart. Positive testing for antiphospholipid antibodies includes the detection of lupus anticoagulant (LAC), medium to high titers of anticardiolipin IgG or IgM antibodies, and titers of anti-B2 glycoprotein-1 antibodies upward of the 99th percentile (22).

Screening for Inherited Thrombophilia

The decision to include screening for inheritable thrombophilias in RPL is not straightforward. Causality between these conditions and adverse pregnancy outcomes early in gestation has not been established and the cost-effectiveness of ordering the thrombophilia testing panel in the RPL evaluation is questionable. Nevertheless, one may consider inclusion of this laboratory screening in RPL, particularly when additional risk factors for coagulopathy are supported by the patients' personal or familial history, or in patients with recurrent late fetal loss (>10 weeks) or with evidence of placental ischemia, infarction,

or thrombosis. Testing should be limited to screening for abnormalities associated with thromboembolic events and these include testing for Factor V Leiden gene mutation, prothrombin G20210A gene mutation, protein C and protein S deficiency via functional activity assays, and antithrombin III levels. Insufficient evidence exists to link hyperhomocysteinemia or methylene tetrahydrofolate reductase deficiency with RPL or VTE and therefore testing for these is not currently recommended.

MANAGEMENT

Anatomic Factors

An improvement in obstetrical outcome following surgical correction of uterine anomalies has been best established in cases of uterine septi (Table 14.2). Uterine septi are the most commonly diagnosed congenital uterine anomalies associated with early pregnancy loss and have been found to confer a risk of RPL of up to 79% (11). Hysteroscopic metroplasty has been shown to decrease the chance of pregnancy loss to <15% and increase the chance of live birth from <20% to 35–80% (6,10). In cases of incidental diagnosis of uterine septi, it is not unreasonable to consider hysteroscopic myomectomy for prevention of pregnancy loss, although this approach is not universally advocated. Patients with Asherman's syndrome similarly benefit from surgical intervention via hysteroscopic adhesiolysis, which increases the chance for live birth and reduces rates of first- and second-trimester losses. The outcomes after hysteroscopic adhesiolysis are associated with severity of disease. The term pregnancy rate after surgical intervention may be upward of 81% and 66% for mild [American Fertility Society (AFS) Stage I] and moderate (AFS Stage II) disease, respectively. Given the partially irrecoverable losses of endometrial function in Asherman's syndrome, relatively high rates of pregnancy failure and relatively low chance for live birth (≤32%) are observed in patients with severe disease (AFS Stage III) after successful surgical resection (6). In cases of polyps and fibroids, the link between etiology is less well established and decreased pregnancy loss rates have been demonstrated, but not consistently, in studies examining the impact of open myomectomy, hysteroscopic myomectomy, and hysteroscopic polylpectomies on RPL (6).

Table 14.2 Treatment Options for Recurrent Pregnancy Loss

Uterine anomalies	Uterine septum	Hysteroscopic metroplasty
	Polyps	Polypectomy or myomecty via laparoscopy or laparotomy
	Leiomyomas	
	Asherman's syndrome	Hysteroscopic adhesiolysis
Chromosomal abnormalities	Sporadic aneuploidy	Preimplantation genetic screening
	Parental chromosomal abnormality	
Endocrinopathies	Hypothyroidism	Levothyroxine
	Diabetes	Metformin, insulin, other
	Hyperprolactinemia	Bromocriptine or cabergoline
	Diminished ovarian reserve	Ovarian stimulation with FSH, IVF
Autoimmune	Antiphospholipid syndrome	Heparin (prophylactic dosing)
		Aspirin (low dose)
Inherited thrombophilia	Factor V Leiden gene mutation	Anticoagulation in setting of VTE history
	Prothrombin G20210A gene mutation	
	Protein C deficiency	
	Protein S deficiency	
	Antithrombin III deficiency	
Infectious	Cervicitis	Antibiotics as appropriate
Other	Celiac disease	Treat underlying disorder
	Obesity	
	Teratospermia	

Abbreviations: FISH, flourescent in situ hybridization; VTE, venothromboembolism.

Genetic Factors

Preimplantation genetic screening (PGS) is an option for couples with RPL due to aneuploidy. The concept is to screen embryos at the cleavage stage via biopsy to remove one blastomere from the day-3 six- to eight-cell embryo, test for euploidy employing fluorescent in situ hybridization (FISH), CGH, or other technology, and transferring euploid embryos at the day 5 to 6 blastocyst stage. While complete outcome data for newer technologies such as CGH are still accumulating, in cases of sporadic aneuploidy, clear evidence that PGS increases live birth rates has not been established. This may be because the biopsy cell does not always represent the embryo's clear permanent make-up due to cellular mosaicism, combined with the embryo's inherent ability to undergo some self-correction to demote aneuploid cells away from essential embryonic development pathways. Nevertheless, the benefit of employing PGS in cases of RPL include shortened time to pregnancy, increased implantation rates, and decreased loss rate, all of great benefit to the patient or couple who has already suffered two or more losses during their time trying to conceive (23). Cost analysis is an additional factor for the patient and the physician to consider before pursuing PGS. Cost-effectiveness studies have demonstrated a potential benefit of PGS when PGS is simply added to preexisting indications for IVF and when maternal age is 35 years or less. PGS combined with IVF may prove to be cost-prohibitive for the patient or couple conceiving spontaneously without difficulty or in couples with advanced maternal age or previously demonstrated high rate (>65%) of embryonic aneuploidy (9). Nevertheless, both patients who consider PGS and those who opt to forego this technological intervention face a favorable prognostic outlook, with a 63% to 71% chance of live birth without intervention. This data has been reproduced widely and supports the benefits of natural selection compared to technological intervention as a possible, and perhaps preferred, treatment algorithm option in these RPL cases (24).

Endocrinopathies

Although the extent to which endocrine dysfunction directly contributes to early pregnancy loss is not known, correction of underlying clinical or subclinical endocrinopathies is intuitive not only in hopes of minimizing the risk of early pregnancy loss but also in optimizing general endocrine health as a woman embarks on a pregnancy. Hyperthyroid disease should be fully evaluated for underlying pathology including nodules, cancer, and Graves' disease and treated appropriately. In clinical hypothyroidism, levothyroxine treatment has been well established as a means to minimize adverse pregnancy outcomes of miscarriage and preterm birth. While not firmly established, levothyroxine treatment of autoimmune and subclinical hypothyroidism may also improve pregnancy outcomes and reduce pregnancy loss and RPL (12). Levothyroxine dosing is based on weight and effect to achieve a TSH of above 0.4 mIU/L and less than 2.5 mIU/L. Given the increased thyroid hormone demands of pregnancy, increasing the levothyroxine dose by 33% during early pregnancy is appropriate.

Dopamine agonists, bromocriptine or cabergoline, may be used to normalize elevated prolactin levels and discontinued once pregnancy occurs. Both medications appear to be nonteratogenic. As more pregnancy safety data is available, many providers favor bromocriptine use for treatment of hyperprolactinemia when pregnancy is anticipated.

Glucose intolerance and diabetes may be managed by diet and exercise and pharmacologically as needed to achieve normal fasting-glucose levels and HbA1c levels prior to conception.

Thrombophilias

At this time, a connection between inherited thrombophilias and early pregnancy loss has not been firmly established nor has a reduction in subsequent losses been demonstrated through anticoagulation. While still an area of debate, most guidelines, including those of the American College of Gynecologists(ACOG), dissuade from anticoagulation prophylaxis in cases of early RPL with underlying inheritable thrombophilia due to the relative risk of treatment complication and the lack of proven benefit (16,25,26).

Autoimmune Phenomena

Substantial data has supported the benefits of anticoagulation in cases of APS and prior adverse pregnancy outcomes including RPL. On the basis of randomized control trials and meta-analyses of available literature, the largest reduction in risk for RPL or other adverse pregnancy outcomes has been observed with a combination of heparin and aspirin. Therefore, at the present time, patients with APS should begin unfractionated or low molecular weight heparin at prophylactic dosing plus low-dose aspirin with the diagnosis of pregnancy (27–29). The use of intravenous immunoglobulin or other immunomodulators for suspected autoimmune-mediated pregnancy loss is not recommended as a consistent benefit has not been demonstrated (30).

Counseling

RPL can be an emotionally and psychologically devastating condition for many patients. The uncertainty of etiology and potential for recurrence can be truly unsettling and may prevent individuals from attempting to conceive. It is equally likely for patients, in desperation, to adopt any number of superstitious behaviors or request unfounded testing or treatments. While many of these activities may provide some comfort, they also have potential for harm. It is essential to provide a careful explanation of what evidence exists for particular recommendations as well as identify the patient's specific concerns and anxieties. It is also highly recommended that a mental health professional be available for additional counseling.

PROGNOSIS

Fortunately, the majority of patients with RPL achieve their goal of having a healthy child, with overall chance of subsequent successful pregnancy of 65%. The challenge, no doubt, is helping patients through the difficult process of getting to that goal, while supporting those patients who must endure the potentially devastating impact of being in the 35% who are not successful.

REFERENCES

1. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril 2008; 90(5 suppl):S60.
2. Rai R, Regan L. Recurrent miscarriage. Lancet 2006; 368(9535):601–611.
3. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril 2010; 93(4):1234–1243.
4. Tang AW, Quenby S. Recent thoughts on management and prevention of recurrent early pregnancy loss. Curr Opin Obstet Gynecol 2010; 22(6):446–451.
5. Branch DW, Gibson M, Silver RM. Clinical practice. Recurrent miscarriage. N Engl J Med 2010; 363(18):1740–1747.
6. Taylor E, Gomel V. The uterus and infertility. Fertil Steril 2008; 89(1):1–16.
7. Porter TF, Scott JR. Evidence-based care of recurrent miscarriage. Best Pract Res Clin Obstet Gynaecol 2005; 19(1):85–101.
8. Reichman DE, Laufer MR. Congenital uterine anomalies affecting reproduction. Best Pract Res Clin Obstet Gynaecol 2010; 24:193–208.
9. Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2011:1191–1220.
10. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertil Steril 1996; 66:24–29.
11. Ford HF, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol 2009; 2(2):76–83.
12. Reid SM, Middleton P, Cossich MC, et al. Intervention for clinical and subclinical hypothyroidism in pregnancy. Cochrane Database Syst Rev 2010; 7:CD007752.
13. Toulis KA, Goulis DG, Venetis CA, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. Eur J Endocrinol 2010; 162(4): 643–652.
14. Haas DM, Ramsey PS. Progesterone for preventing miscarriage. Cochrane Database Syst Rev 2008; 16(2):CD003511.
15. Said JM, Higgins JR, Moses EK, et al. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. Obstet Gynecol 2010; 115(1):5–13.

16. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 113: Inherited thrombophilias in pregnancy. Obstet Gynecol 2010; 116(1):212–222.
17. Branch DW. The truth about inherited thrombophilias and pregnancy. Obstet Gynecol 2010; 115(1):2–4.
18. Rey E, Kahn SR, David M, et al. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003; 361:901–908.
19. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 118: Antiphospholipid syndrome. Obstet Gynecol 2011; 117(1):192–199.
20. Ruder EH, Hartman TJ, Goldman MB. Impact on oxidative stress on female fertility. Curr Opin Obstet Gynecol 2009; 21(3):219–222.
21. Parker VJ, Douglas AJ. Stress in early pregnancy: maternal neuro-endocrine-immune response and effects. J Reprod Immunol 2010; 85(1):86–92.
22. Lim W. Antiphospholipid antibody syndrome. Hematol Am Soc Hematol Educ Program 2009:233–239.
23. Fischer J, Colls P, Escudero T, et al. Preimplantation genetic diagnosis (PGS) improves pregnancy outcome for translocation carriers with a history of recurrent losses. Fertil Steril 2010; 94(1):283–289.
24. Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod 2006; 21(4):1076–1082.
25. Benedetto C, Marozio L, Tavella AM, et al. Coagulation disorders in pregnancy: acquired and inherited thrombophilias. Ann N Y Acad Sci 2010; 1205:106–117.
26. Mantha S, Bauer KA, Zwicker JI. Low molecular weight heparin to achieve live birth following unexplained pregnancy loss: a systematic review. J Thromb Haemost 2010; 8:263–268.
27. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010; 362(17):1586–1596.
28. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstet Gynecol 2010; 115(6):1256–1262.
29. Mak A, Cheung MW, Cheak AA, et al. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospolipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology 2010; 49:281–288.
30. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev 2006; 2:CD000112.

15 Modern management of ectopic pregnancy

David A Ryley

The diagnosis and management of ectopic pregnancy continue to be a challenge for the gynecologist. Infertility is a risk factor for the development of an ectopic pregnancy. Underlying tubal disease is the mitigating cause in most cases. The management of this clinical entity has changed dramatically over the years because of earlier diagnosis and the addition of medical treatment with methotrexate. This chapter provides an overview of the clinical problem and current management recommendations.

EPIDEMIOLOGY

Approximately 1% to 2% of all pregnancies do not implant in the uterine cavity and are ectopic in location. The majority (95%) of ectopic pregnancies are located in the fallopian tube and the remainder (5%) in the ovary, cervical canal, or the abdominal cavity. Risk factors for an ectopic pregnancy include a previous pelvic infection, current or previous use of an intrauterine device (IUD), history of pelvic inflammatory disease, tubal reconstructive surgery, infertility, increased maternal age, in utero exposure to diethylstilbestrol, and smoking. Women who have had a previous ectopic pregnancy have a 10% chance of a recurrent ectopic pregnancy with a future pregnancy. These women should be counseled that they should make arrangements to have a pregnancy test if they have an abnormal menstrual period, intermenstrual bleeding, or worsening lower abdominal pain.

CLINICAL PRESENTATION OF AN ECTOPIC PREGNANCY

The classic symptoms of an ectopic pregnancy are amenorrhea, unilateral abdominal pain, and abnormal vaginal bleeding. However, these symptoms only result when the ectopic pregnancy is at an advanced stage. Monitoring with vaginal ultrasonography and serial β-hCG titers during the early part of pregnancy has helped us to diagnose an ectopic pregnancy at an early stage before symptoms develop. An ectopic pregnancy can be diagnosed when the vaginal ultrasound demonstrates the presence of a gestational sac outside the uterine cavity. A presumed ectopic can be considered when there is lack of visualization of a gestational sac in the uterine cavity by vaginal ultrasound at six weeks of gestation or when the β-hCG titer is >2000 mIU/mL. An ectopic pregnancy should also be suspected when the β-hCG titers are not rising normally.

As a general rule, the mean doubling time for the β-hCG titer in a normal pregnancy is 48 hours but there is variability in the rise of β-hCG titer (1,2). In a recent publication, Barnhart et al., followed the β-hCG titers in 287 women who were confirmed to have a viable intrauterine pregnancy (3). Using a 99% CI, they concluded that viable pregnancies have at least a 53% increase in β-hCG titer in two days and an 88% increase in three days (Table 15.1). If the rate of rise of β-hCG is below the 99th percentile, then one can safely conclude that the pregnancy is not viable. Studies have confirmed that abnormal pregnancies generally are associated with abnormal rising titers. However, approximately 20% of ectopic pregnancies are associated with normal rising β-hCG levels (1).

MANAGEMENT OPTIONS

The clinician now has several treatment options to choose from for the management of an ectopic pregnancy. The appropriate treatment depends on the presentation and other considerations.

The Role of a D&C

When an abnormal pregnancy is diagnosed and the ultrasound fails to confirm either an intrauterine pregnancy or an ectopic pregnancy, should a dilatation and curettage (D&C) be performed prior to administration of the methotrexate? The advantage of going directly to

Table 15.1 The 50th Percentile Is the Expected Median Increase for a Viable Intrauterine Pregnancy

Percentile	Relative increase in β-hCG titers from baseline			
	1 day later	2 days later	3 days later	4 days later
1st	1.24	1.53	1.88	2.33
5th	1.31	1.71	2.23	2.91
10th	1.35	1.81	2.44	3.28
15th	1.37	1.89	2.59	3.56
50th	1.50	2.24	3.35	5.00
85th	1.63	2.65	4.32	7.04
90th	1.66	2.76	4.59	7.63
95th	1.71	2.93	5.02	8.60
99th	1.81	3.28	5.94	10.76

The first percentile is the slowest expected increase for a normal pregnancy (99% of pregnancies will have a more rapid increase).
Source: Modified from Ref. 3.

methotrexate is that it can be done more quickly and the patient avoids a surgical procedure. The advantages of performing a D&C first are that the clinician can more confidently make the diagnosis of an ectopic pregnancy and the D&C may resolve an unsuspected missed abortion. A publication by Barnhart et al. sheds further light on the issue. In this retrospective study, they reported on 112 patients who had abnormally rising β-hCG titers and an inconclusive ultrasound. All these patients underwent a D&C. The investigators reported that 46% of women with titers >2000 mIU/mL and 31.2% with titers <2000 mIU/mL were confirmed to have a nonviable intrauterine pregnancy (4). This study supports a good argument that a D&C should be performed prior to initiating medical treatment. However, one problem is that it may take several days before the final pathology report is made available. A solution is that a β-hCG titer can be checked the day following the D&C. If the titer rises or fails to decrease by 15%, then an ectopic pregnancy is strongly suggested (5).

Observation

Patients who are suspected of having an ectopic pregnancy and are clinically stable should have the β-hCG titer repeated in two to three days. If the titer decreases, then the ectopic pregnancy could be undergoing spontaneous resolution and observation is the indicated treatment, as long as the titers continue to decrease and the patient remains clinically stable. Spontaneous resolution is more likely to occur when the β-hCG titers are lower (6). A previous study confirmed that 90% of abnormal pregnancies with β-hCG titers less than 200 mIU/mL resolved without intervention (7). It is important to realize that even if the titers are decreasing, tubal rupture can still occur. For this reason, any complaints of abdominal pain experienced by the patient should be investigated.

Medical Treatment with Methotrexate

In the past, the treatment for an ectopic pregnancy was almost exclusively a surgical approach. Over 15 years ago, methotrexate was introduced as a medical treatment for this condition. Initially, methotrexate was administered to women who had persistent trophoblastic tissue that remained in the fallopian tube following a salpingostomy. There have been several published studies demonstrating the effectiveness and safety of methotrexate when used as primary treatment for an ectopic pregnancy (8). In today's medical practice, medical treatment for an ectopic pregnancy offers an alternative to surgery (9–12).

Methotrexate can be administered by single injection (with repeat weekly injections if needed) or by the multidose protocol. In the multidose protocol, on alternative days methotrexate and citrovorum rescue factor are given. The single-dose protocol has obvious advantages but there has been some debate as to whether it is as efficacious as the multidose protocol. In a previous meta-analysis, the multidose regimen was concluded to be more effective (13). In a recent study, Lipscomb et al. reported on 643 patients who were treated with

methotrexate for ectopic pregnancy. They reported that there was no statistical difference in the success rates following the single-dose protocol versus the multidose protocol (90% vs. 95%, $P = 0.18$) (14).

Action

Methotrexate is a folic acid antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of the purine nucleotide thymidilate and amino acids, serine and methionine. Thus, methotrexate interferes with deoxyribonucleic acid (DNA) synthesis and cell multiplication. Actively proliferating trophoblastic tissue is sensitive to this effect of methotrexate, which forms the rationale for its use in the treatment of ectopic pregnancy as well as gestational trophoblastic disease.

Indications for Methotrexate Administration

A woman may be considered a candidate for methotrexate administration if she has any of the following indications:

1. Is interested in future fertility;
2. Has a documented gestational sac outside of the uterine cavity;
3. Has an ectopic pregnancy in a location (i.e., the cervix, cornua, and ovary) that is not amenable to surgical treatment;
4. Is a poor operative risk;
5. Has a suspected ectopic pregnancy:
   a. abnormally rising β-hCG titers;
   b. no evidence of an intrauterine pregnancy by vaginal ultrasound when the β-hCG titer has reached 2000 mIU/mL and/or at six weeks of gestation;
   c. no villi identified in the tissue removed with a D&C and rising or plateauing β-hCG titers during the postoperative period.
6. Has rising or plateauing β-hCG titers following a linear salpingostomy.

Contraindications for Methotrexate Administration

A woman is not considered a candidate for methotrexate administration if she has any of the following:

1. Is clinically unstable (decreased hematocrit, evidence of hemorrhage, or worsening abdominal pain);
2. Has impaired renal and liver function, thrombocytopenia, or leukopenia;
3. Has a coexisting viable intrauterine pregnancy;
4. Is noncompliant;
5. Is breast-feeding;
6. Has any of the following:
   a. History of alcohol abuse
   b. Active pulmonary disease
   c. Peptic ulcer disease
   d. Liver disease
7. Has gestational sac (>3.5 cm), β-hCG titer >5000 mIU/mL, or fetal heart activity (relative contraindications).

Pretreatment Evaluation

The following are prerequisites that must be met before treatment with methotrexate can be considered:

1. A medical consultation with a history and physical examination
2. A vaginal ultrasound examination

3. Baseline laboratory work, including
   a. blood type and screen with the administration of Rhogam®, if indicated;
   b. CBC;
   c. platelet count;
   d. SGOT;
   e. β-hCG titer;
   f. creatinine.
4. Determination of the patient's height and weight
5. A signed consent form prior to the initiation of treatment

Administration

Methotrexate is a chemotherapeutic drug and special care must be taken with the administration and handling of this medication. We recommend that you talk about these issues with a pharmacist before using this medication. The standard dose of methotrexate to be administered is 50 mg/m^2. The dose is based on surface area (m^2), which is calculated from the patient's height and weight. We recommend that the pharmacist verify the surface-area calculation and the dose to be administered. The injection is administered by intramuscular injection and is well tolerated by the patient.

Patient Instructions

Following the injection, and until there is resolution, the patient should be instructed to avoid the following:

- Alcohol
- Folic acid and vitamins that contain folic acid
- Exposure to the sun, sun lamp, and tanning salons
- Nonsteroidal anti-inflammatory agents
- Immunizations
- Intercourse
- Contraception for two months following resolution

Postinjection Follow-up

Following the administration of methotrexate, a repeat β-hCG titer should be measured four and seven days after the injection. In most cases, the titer obtained four days after the injection will continue to rise when compared to the titer obtained on the day of injection. The delayed effectiveness following the injection results from the gradual incorporation of methotrexate into the cell cycle of the trophoblastic tissue.

- If there is >15% decline between titers postinjection days 4 and 7, then weekly β-hCG titers are obtained and followed until they are negative.
- If there is <15% decline between titers postinjection days 4 and 7, a second dose of methotrexate 50 mg/m^2 can be administered and the titers are again assessed on days 4 and 7 after the injection.
- If there is *less* than a 15% decline between titers on posttreatment days 4 and 7, a third dose of methotrexate 50 mg/m^2 can be administered.
- Alternatively, laparoscopic evaluation may be considered (see section "Surgical Treatment").

Because of the risk of tubal rupture, intercourse should be avoided until the β-hCG titer has become negative. However, those patients who choose to have intercourse should be counseled to use contraception.

The methotrexate protocol for the treatment of an ectopic pregnancy described above is referred to as the "single-dose" protocol, and is more commonly utilized than the alternative "multidose" regimen. The latter involves the intramuscular injection of up to four doses of

methotrexate (1 mg/kg) every other day alternating with the intramuscular injection of lucovorin rescue factor (0.1 mg/kg folinic acid). The treatment is continued until the serum β-hCG decreases by 15% (15). A meta-analysis, published in 2003, compared the two protocols and determined that the multidose regimen was more effective (13). The odds ratio (OR) of failed medical management of the single dose compared to the multidose regimen was 1.71 (CI:1.04–2.82). However, subsequent studies suggest that the success rates of the two protocols are similar, and the single-dose protocol is typically the favored approach among clinicians due to its simplicity and low side-effect profile (14).

Side Effects

Side effects usually do not appear until two to seven days after administration. Side effects include nausea, vomiting, stomatitis, diarrhea, dizziness, and loss of appetite. Rarely, methotrexate can cause leukopenia and/or thrombocytopenia. Other very uncommon side effects include hair loss, skin rash, dizziness, and liver dysfunction. Abdominal pain is another symptom that can be noted after administration of the drug (11,12); this symptom is most likely the result of separation of the ectopic pregnancy from the tube. Others have theorized that some abdominal symptoms may be secondary to a transient toxic effect of methotrexate on the gastrointestinal tract. However, depending on the severity of the pain, the patient should be evaluated to rule out tubal rupture with a pelvic examination, vaginal ultrasound, and a β-hCG titer.

Clinical Results

There have been several reports investigating the use of methotrexate for the treatment of ectopic pregnancy. The largest study reported is on 320 women who underwent methotrexate treatment for an ectopic pregnancy (16). Following medical treatment, 91% of patients had resolution of the ectopic pregnancies. A total of 81% responded to one injection, 17% required two injections, and 2% required three injections. The mean time until resolution was five weeks. The medical treatment was well tolerated with few side effects. The following factors were not predictors of success: the woman's age or parity, the size of the ectopic pregnancy, and the presence or absence of fluid in the peritoneal cavity. Fetal heart activity was present in 12% of the successfully treated cases and 30% of those in which methotrexate treatment was unsuccessful. Regression analysis confirmed that only the initial β-hCG titer was predictive of success, which is presented in Table 15.2. The authors concluded that methotrexate could be considered when the β-hCG titer was up to 10,000 mIU/mL. However, other reports suggest that a more conservative approach is warranted and medical treatment should only be considered when the titer is <3000 mIU/mL (17,18). Methotrexate failures and tubal rupture are more likely in cases when fetal heart activity is present or the β-hCG titers were rising normally pretreatment or the titers continue to rise following the first course of methotrexate.

Conclusion: Medical Therapy

Medical treatment with methotrexate offers another treatment option for patients with ectopic pregnancies. In selected cases, it has demonstrated its efficacy and safety, and it is cost effective when compared to a surgical approach.

Table 15.2 The Success of Methotrexate Treatment Related to Initial β-hCG Titer

Initial β-hCG titer	Success	Failure	Success rate (95% CI)
<1,000	118	2	98% (96–100)
1,000–1,999	40	3	93% (85–100)
2,000–4,999	90	8	92% (86–97)
5,000–9,999	39	6	87% (79–98)
10,000–14,999	18	4	82% (65–98)
≥15,000	15	7	68% (49–88)

Source: Modified from Ref. 16.

Surgical Treatment

Surgical management of an ectopic pregnancy is indicated when medical therapy has failed or is contraindicated (see section "Contraindications for Methotrexate Administration"). Surgery may also be the preferred approach even if the patient is a candidate for methotrexate. It allows a definitive diagnosis to be made. It also provides an opportunity to survey the condition of the other pelvic organs, which is helpful in the management of the patient who has infertility. Finally, if the patient is suffering from a recurrent ectopic pregnancy in the same tube or the patient is undergoing IVF treatment, serious consideration should be given to removing the tube.

Operative intervention is *absolutely* indicated as the initial approach to the treatment of a suspected ectopic pregnancy when the following clinical scenarios are present:

- Hemodynamic instability, that is, hypotension, tachycardia
- High index of suspicion of a pending or recent tubal rupture
- Clinical symptoms of acute peritoneal irritation

Operative intervention is the *preferred* initial approach to treatment when the following clinical scenarios are present:

- Signs of fetal cardiac activity within the adnexal mass
- Serum β-hCG concentrations greater than 5000 mIU/mL
- The confirmation of an adnexal mass measuring greater than 4 cm by transvaginal ultrasound
- The confirmation of free fluid in the cul-de-sac and/or pelvis by transvaginal ultrasound

Laparoscopy Vs. Laparotomy

Conservative surgical treatment via operative laparoscopy is generally preferred to laparotomy, except for those cases in which the patient is unstable due to severe hypovolemia resulting from hemorrhage.

The advantages of laparoscopy over laparotomy include shorter hospital stays, quicker recovery, reduced blood loss and adhesion formation, and reduced cost (19–21). Comparison of clinical outcomes between laparoscopy and laparotomy for the treatment of ectopic pregnancy shows similar rates of subsequent tubal patency (80%–90%), intrauterine pregnancy (55%–75%), and recurrent ectopic pregnancy (10%–15%) (17).

Laparoscopic Salpingostomy Vs. Salpingectomy

Eighty percent of ectopic pregnancies are located in the ampullary portion of the affected tube. The preferred surgical treatment of an unruptured ampullary ectopic pregnancy is a laparoscopic salpingostomy.

Indications for laparoscopic salpingectomy include the following:

- Rupture and extensive damage to the involved fallopian tube
- Inability to achieve hemostasis of the involved fallopian tube
- Recurrent ectopic pregnancy in the involved fallopian tube
- The patient has clearly indicated that she has completed her childbearing

In a prospective analysis of 143 laparoscopic procedures for the treatment of ectopic pregnancy, the authors determined that the subsequent intrauterine pregnancy rates for laparoscopic salpingostomy (60%) and laparoscopic salpingectomy (54%) were not significantly different (22). However, a retrospective cohort study determined that the more conservative approach is more likely to preserve subsequent fertility. A multivariate analysis from this study showed a three-year spontaneous intrauterine pregnancy rate following laparoscopic salpingostomy of 62%. The rate following laparoscopic salpingectomy was 38% ($P < 0.001$) (23).

Recurrent ectopic pregnancy rates following operative laparoscopic salpingostomy are 12% to 15.5%, the majority of these (85%) occur in the ipsilateral fallopian tube (24,25). When

the contralateral fallopian tube is left in situ, recurrence rates after laparoscopic salpingectomy are similar, but slightly lower at 9.8% (26).

Certain factors have a negative impact on a patient's subsequent fertility following conservative operative treatment of an ectopic pregnancy. A history of either infertility, salpingitis, prior ectopic pregnancy, or a solitary remaining fallopian tube are associated with subsequent intrauterine pregnancy rates that are significantly lower than in patients without these characteristics (88.7% vs. 56%, $P < 0.001$) (24). Additionally, the presence of ipsilateral and contralateral periadnexal adhesions has a negative impact on subsequent successful pregnancy and conception rates following operative treatment of ectopic pregnancy by laparoscopic salpingostomy. In those patients found to have ipsilateral adhesions, the subsequent intrauterine pregnancy rate was significantly lower than the rate seen in patients with a normal ipsilateral fallopian tube (67.5% vs. 45.7%, $P < 0.02$). Patients found to have contralateral periadnexal adhesions and a blocked contralateral tube had low subsequent intrauterine pregnancy rates of 21.3%, and high recurrent ectopic rates of 21.3%. If the contralateral fallopian tube was patent, the presence of surrounding adhesions decreased subsequent intrauterine pregnancy rates from 82.8% to 41.9%, $P < 0.001$ (24). These patients may consider in vitro fertilization for future conception, in that cumulative success rates from assisted reproductive technologies for the treatment of tubal factor infertility may exceed the rates cited in this study.

Persistent Ectopic Pregnancy

The most common complication of laparoscopic salpingostomy is a persistent ectopic pregnancy, occurring in 3% to 29% of women who have undergone this conservative surgical approach (26,27). Risk factors for the development of a persistent ectopic pregnancy include

- small ectopic pregnancies, that is, those measuring less than 2 cm;
- early surgical intervention, occurring less than 42 days from the last menstrual period (24);
- preoperative serum β-hCG levels of 3000 mIU/mL or greater (28).

A retrospective cohort study of 147 patients treated surgically for an ectopic pregnancy determined that a decline in the postoperative day 1 serum hCG of <50% from the preoperative value was predictive of a persistent ectopic, with a sensitivity of 42% and specificity of 88%. Declines of less than 50% were associated with an RR of 3.51 (CI 1.25–6.68) for a persistent ectopic gestation (29).

It is imperative for the clinician to inform patients of the risk of having a persistent ectopic subsequent to conservative laparoscopic techniques. The need for postoperative surveillance and potential intervention with methotrexate should be discussed in detail during the preoperative informed consent process.

Postoperative surveillance includes the following:

- Measurement of the serum β-hCG on postoperative day 1
  - A decline of >50% from the preoperative level requires a repeat measurement in seven days.
  - A decline of <50% from the preoperative level requires a repeat measurement on postoperative day 3. Repeat testing is required every three to seven days until the serum hCG levels are no longer detectable.
- Patients with a plateau or rise in the serum β-hCG level are candidates for the single-dose methotrexate regimen (see section "Indications for Methotrexate Administration").

Surgical Vs. Medical Treatment

Success Rates

A randomized prospective trial of 100 patients with laparoscopically confirmed unruptured tubal ectopic pregnancies showed similar success rates between those patients treated with methotrexate versus those who underwent attempted laparoscopic salpingostomy. Although patients with documented fetal heart activity were excluded from the study, the authors did not

limit randomization based on either the initial serum hCG concentration, or on the size of the ectopic gestation. Of the patients allocated for treatment with methotrexate, 82% were successfully treated with one course of treatment and 4% required an additional course of treatment for persistent trophoblast. Surgical intervention was required in 14% of the patients initially treated with methotrexate, the majority of whom required salpingectomy due to tubal rupture. In the group of patients who were randomized to attempted laparoscopic salpingostomy, 72% were successfully treated by this surgical approach. A salpingectomy was required in 8% of these patients, and 20% required methotrexate due to persistent trophoblast. Median serum hCG clearance times in the methotrexate group versus laparoscopic salpingostomy group were not statistically different; 19 days versus 14 days, $P = 0.64$. The outcome measures of tubal preservation and ipsilateral tubal patency were similar between the two groups. The affected tube was preserved in 90% of the patients in the methotrexate group versus 92% in the salpingostomy group. Hysterosalpingograms performed three months after the completion of therapy revealed ipsilateral tubal patency rates in the methotrexate versus laparoscopic salpingostomy groups of 62% versus 66% (rate ratio 0.93, CI: 0.64–1.4) (30). The resulting pregnancy rates following medical or surgical treatment is presented in Table 15.3.

Comparing the reproductive outcomes following methotrexate treatment versus the surgical management of an ectopic pregnancy requires consideration of the potential gonadotoxic potential of the former. A retrospective cohort study of infertile women undergoing IVF suggested that oocyte yields within 180 days of methotrexate treatment of an ectopic pregnancy were lower than those obtained beyond that time frame (31). It appears, as noted in a prospective observational study, that this impact of methotrexate on the ovarian reserve is time limited and reversible (32). Additionally, despite the potential for teratogenicity, pregnancies conceived within six months of methotrexate exposure are at no greater risk of fetal malformations, miscarriage, or adverse pregnancy outcomes (33).

Quality of Life

A randomized prospective trial of patients undergoing treatment for laparoscopically confirmed unruptured ectopic pregnancies investigated the differential impact of methotrexate and laparoscopic salpingostomy on quality of life. The authors noted that patients treated with repeated doses of systemic methotrexate were more likely to have limitations in physical functioning. Their overall quality of life, as determined by health perception, energy level, degree of pain, overall symptom complex, and psychological depression, was deemed to be significantly inferior to that of the patients treated surgically (34). However, in a prospective randomized study comparing single-dose methotrexate with laparoscopic salpingostomy, the researchers noted that the patients treated medically had significantly better physical functioning scores compared to the women who were treated surgically. There were no differences in psychological outcomes between the two treatment groups in this study (35).

Cost-Effectiveness

In an analytical model that accounted for varying resolution rates, complication rates, and cost estimates, researchers determined significant cost savings with single-dose methotrexate treatment protocols compared to the laparoscopic approach. Using meta-analysis results of studies comparing these treatments, the researchers estimated a cost saving of more than $3000 (US dollars in the year 2000) per resolved ectopic pregnancy in those patients treated with the single-dose methotrexate protocol (36) (Table 15.3).

Table 15.3 Fertility After Medical Vs. Surgical Treatment for Tubal Ectopic Pregnancy

	Treatment protocol		
	Methotrexate	Salpingostomy	Salpingectomy
Subsequent intrauterine pregnancies rates	58–61%	62% (3-yr follow-up) 89% (7-yr follow-up)	38% (3-yr follow-up) 66% (7-yr follow-up)
Repeat ectopic pregnancy rate	7–8%	18%	6–28%

The rates reflect the results of various observational studies.
Source: Adapted from Ref. 37.

Unusual Ectopic Pregnancies

As mentioned above, the majority of ectopic pregnancies are located in the ampullary portion of the fallopian tube. Rarer loci include (38)

- Isthmus of the fallopian tube
- Fimbrial end of the fallopian tube
- Uterine cornua/interstitial
- Abdomen
- Ovaries
- Cervix
- Cesarean scar ectopic (39)

Treatment protocols for these clinical scenarios combine surgical and medical approaches. The specific therapy is dependent on the gestational age of the pregnancy and clinical status of the patient.

Heterotopic pregnancies are characterized by an intrauterine pregnancy occurring concomitantly with an ectopic gestation, the vast majority of the ectopics implanting in the ampullary portion of the fallopian tube. The incidence of this condition is dependent on the mode of conception. Rates of 1/10,000 to 1/50,000 are seen among spontaneous pregnancies, versus an incidence of 1% among conceptions resulting from assisted reproductive technologies (40). The treatment is surgical.

CONCLUSION

The increasing proficiency of transvaginal ultrasound combined with the enhanced accuracy of the radioimmunoassay for the β-hCG allows a definitive and early diagnosis of ectopic pregnancy. Treatment options in this setting include conservative medical (systemic methotrexate) and surgical (laparoscopic salpingostomy) approaches that minimize risk, intervention, cost, and time of recuperation. The relative risks and benefits of these treatment protocols with respect to both the success of treatment and restoration of future fertility have been outlined in this chapter. We hope that clinicians will use this information to determine the optimal treatment strategy for their patients.

REFERENCES

1. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. Obstet Gynecol 1981; 58:162–166.
2. Pittaway DE, Reish RL, Wentz AC. Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies. Am J Obstet Gynecol 1985; 152:299–302.
3. Barnhart KT, Sammel MD, Rinaudo PF, et al. Symptomatic patients with an early viable intrauterine pregnancy: hCG curves redefined. Obstet Gynecol 2004; 104:50–55.
4. Barnhart KT, Katz I, Hummel A, et al. Presumed diagnosis of ectopic pregnancy. Obstet Gynecol 2002; 100:505–510.
5. Stovall TG, Ling FW, Carson SA, et al. Nonsurgical diagnosis and treatment of tubal pregnancy. Fertil Steril 1990; 54:537–538.
6. Shalev E, Peleg D, Tsabari A, et al. Spontaneous resolution of ectopic tubal pregnancy: natural history. Fertil Steril 1995; 63:15–19.
7. Korhonen J, Stenman UH, Ylostalo P. Serum human chorionic gonadotropin dynamics during spontaneous resolution of ectopic pregnancy. Fertil Steril 1994; 61:632–636.
8. Lipscomb GH, Stovall TG, Ling FW. Primary care: nonsurgical treatment of ectopic pregnancy. N Engl J Med 2000; 343:1325–1329.
9. Corsan GH, Karacan M, Qasim S, et al. Identification of hormonal parameters for successful systemic single-dose methotrexate therapy in ectopic pregnancy. Hum Reprod 1995; 10:2719–2722.
10. Henry MA, Gentry WL. Single injection of methotrexate for treatment of ectopic pregnancies. Am J Obstet Gynecol 1994; 171:1584–1587.
11. Stika CS, Anderson L, Frederiksen MC. Single dose methotrexate for the treatment of ectopic pregnancy: Northwestern Memorial Hospital three-year experience. Am J Obstet Gynecol 1996; 174:1840–1846.
12. Stovall TG, Ling FW. Single dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993; 168:1759–1765.

13. Barnhart KT, Gosman G, Ashby R, et al. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol 2003; 101:778–784.
14. Lipscomb GH, Givens VM, Meyer NL, et al. Comparison of multidose and single-dose methotrexate protocols for the treatment of ectopic pregnancy. Am J Obstet Gynecol 2005; 192:1844–1848.
15. Ory SJ, Villanueva AL, Sand PK, et al. Conservative treatment of ectopic pregnancy with methotrexate. Am J Obstet Gynecol 1986; 154:1299–1306.
16. Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999; 341:1974–1978.
17. Hajenius PJ, Mol BW, Bossuyt PM, et al. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev 2000; (1):CD000324.
18. Gamzu R, Almog B, Levin Y, et al. Efficacy of methotrexate treatment in extrauterine pregnancies defined by stable or increasing human chorionic gonadotropin concentrations. Fertil Steril 2002; 77:761–765.
19. Brumsted J, Kessler C, Gibson C, et al. A comparison of laparoscopy and laparotomy for the treatment of ectopic pregnancy. Obstet Gynecol 1988; 71:889–892.
20. Lundorff P, Hahlin M, Kallfelt B, et al. Adhesion formation after laparoscopic surgery in tubal pregnancy: a randomized trial versus laparotomy. Fertil Steril 1991; 55:911–915.
21. Vermesh M, Silva PD, Rosen GF, et al. Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomized clinical trial of laparoscopy versus laparotomy. Obstet Gynecol 1989; 73:400–403.
22. Silva PD, Schaper AM, Rooney B. Reproductive outcome after 143 laparoscopic procedures for ectopic pregnancy. Obstet Gynecol 1993; 81:710–715.
23. Job-Spira N, Bouyer J, Pouly J. Fertility after ectopic pregnancy: first results of a population-based cohort study in France. Hum Reprod 1996; 11:99–104.
24. Pouly JL, Chapron C, Manhes H, et al. Multifactorial analysis of fertility after conservative laparoscopic treatment of ectopic pregnancy in a series of 223 patients. Fertil Steril 1991; 56:453–460.
25. Yao M, Tulandi T. Current status of surgical and nonsurgical management of ectopic pregnancy. Fertil Steril 1997; 67:421–433.
26. Seifer DB. Persistent ectopic pregnancy: an argument for heightened vigilance and patient compliance. Fertil Steril 1997; 68:402–403.
27. Seifer DB, Gutmann JN, Doyle MB, et al. Persistent ectopic pregnancy following laparoscopic linear salpingostomy. Obstet Gynecol 1990; 76:1121–1125.
28. Lundorff P, Hahlin M, Sjoblom P, et al. Persistent trophoblast after conservative treatment of tubal pregnancy: prediction and detection. Obstet Gynecol 1991; 77:129–133.
29. Spandorfer SD, Sawin SW, Benjamin I, et al. Postoperative day 1 serum human chorionic gonadotropin level as a predictor of persistent ectopic pregnancy after conservative surgical management. Fertil Steril 1997; 68:430–434.
30. Hajenius PJ, Engelsbel S, Mol BWJ, et al. Randomized trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. Lancet 1997; 350:774–779.
31. McLaren JF, Burney RO, Milki, AA, et al. Effect of methotrexate exposure on subsequent fertility in women undergoing controlled ovarian stimulation. Fertil Steril 2009; 92:515–519.
32. Oriol B, Barrio A, Pacheco A, et al. Systemic methotrexate to treat ectopic pregnancy does not effect ovarian reserve. Fertil Steril 2008; 90:1579–1582.
33. Svirsky R, Rozovski U, Vaknin Z, et al. The safety of conception occurring shortly after methotrexate treatment of an ectopic pregnancy. Reprod Toxicol 2009; 27:85–87.
34. Nieuwkerk PT, Hajenius PJ, Ankum WM, et al. Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy, part I: impact on patients' health related quality of life. Fertil Steril 1998; 70:511–517.
35. Sowter M, Farquhar C, Petrie K, et al. A randomized trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy. Br J Obstet Gynecol 2001; 108:192–203.
36. Morlock RJ, Lafata JE, Eisenstein D. Cost-Effectiveness of single-dose methotrexate compared with laparoscopic treatment of ectopic pregnancy. Obstet Gynecol 2000; 95:407–412.
37. Farquhar CM. Ectopic pregnancy. Lancet 2005; 366:583–591.
38. Breen JL. A 21 year survey of 654 ectopic pregnancies. Am J Obstet Gynecol 1970; 106:1004–1019.
39. Maymon R, Halperin R, Mendlovic S, et al. Ectopic pregnancies in Caesarean section scars: the 8 year experience of one medical centre. Hum Reprod 2004; 19:278–284.
40. Rizk B, Tan SL, Morcos S, et al. Heterotopic pregnancies after in vitro fertilization and embryo transfer. Am J Obstet Gynecol 1991; 164:161–164.

16 Integrating quality management into a fertility practice

Michael M Alper

What is a quality management system (QMS) and what does it have to do with an infertility practice? If you have never heard the term QMS, you are not alone. I had not a clue what it meant just a few years ago. And I certainly had no idea of its relevance to medicine. The purpose of this chapter is not to give a detailed analysis of a QMS, but rather to understand how it relates (in simple terms) to what we do every day in our practice of medicine.

The underlying purpose of a QMS is simple—"Say what you do and do what you say." A QMS provides the tools to clearly delineate what everyone's responsibility is within your organization. It gets down to the core of your corporate essence—what you are about, why you do what you do, how you do it, and how you can do things better. The system is derived from the organization itself, and it is not something that is imposed from the outside. Therefore, part of the fun of developing a QMS is the creation of it. Sure, it is work. But it is also worthwhile as I hope to explain in this chapter.

WHY IS QUALITY MANAGEMENT IMPORTANT?

Let me illustrate an example for the need of a QMS. I was visiting a highly respected in vitro fertilization (IVF) practice in the northeast United States. I asked the medical director what protocol they followed to replace frozen embryos. He precisely and carefully reviewed their technique to accomplish this. I then asked him for a written summary so that I could discuss his technique with my colleagues back in Boston. After shuffling through his files, he came up with an overphotocopied and illegible summary of the protocol. He apologized and commented that "most of what we do is in our heads." So, what is wrong with this picture? How are new colleagues supposed to learn existing protocols at this IVF center? How do the nurses know what is expected of them? How can one keep track of changes in the protocol to observe resultant changes in outcome? Documentation is the cornerstone of a QMS, and this example illustrates the dire need of a QMS in an infertility practice.

IVF centers are complex organizations. They involve the integration of many specialized professionals including physicians, nurses, scientists, administration, and others. In fact, it is a "mini hospital." These different entities have to work well as a team (Fig. 16.1). They need to communicate well, since a change in one area can quickly affect the others. The organization falls apart if any one area fails. A QMS assures that the infrastructure is set for all the players in the organization to communicate and achieve the common goals of the organization. Failure of an organization to function properly results in potentially serious errors at the very worst or corporate dysfunction at the very least.

ISO—AN EXAMPLE OF QUALITY MANAGEMENT SYSTEM

The International Standard Organization called "ISO" is the most recognized standard for a QMS. This is a global organization with regional organizations in most countries to represent the international standard. ISO governs thousands of standards. For example, the standards for making a part such as a bolt needs to be standardized so that a particular sized bolt from one company A could replace another from company B. So, these standards exist for several thousand products to keep some uniformity. Another important function of ISO is to develop manufacturing standards. For example, if you are designing an aircraft for Boeing and want to install a particular aircraft part, you would purchase it only from a manufacturer that is ISO certified. This is one way to govern that the part comes from a company that meets certain manufacturing standards. Similarly, ISO standards exist for service industries. These

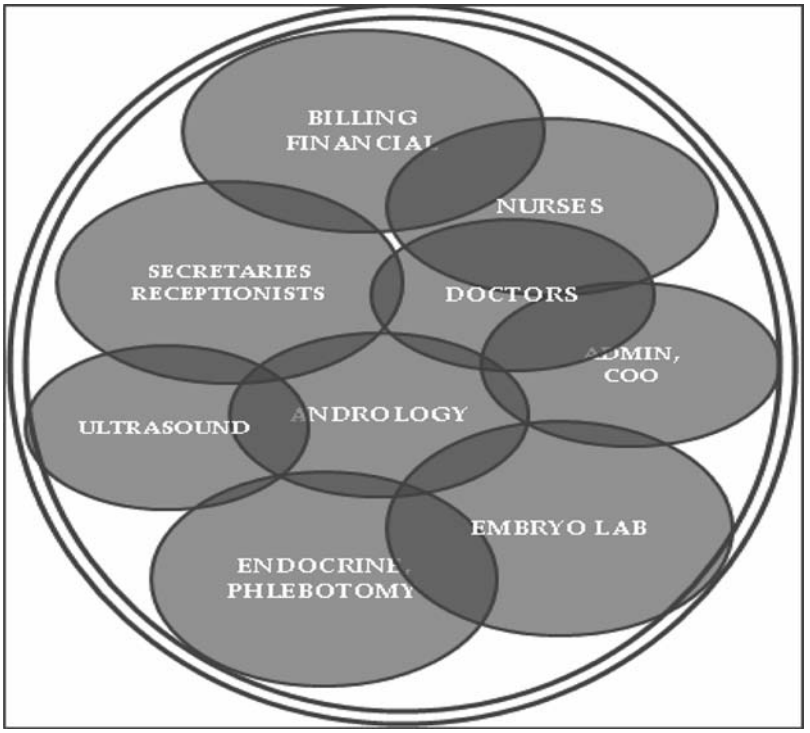

Figure 16.1 The IVF team must be a coordinated effort of many disciplines that must all communicate with one another. *Abbreviation*: IVF, in vitro fertilization.

How to get ISO-Certified:

1. Know the ISO standard
2. Document a quality management system
3. Implement the system
4. Be surveyed (assessed) by an accredited registrar
5. Be issued a Certificate of Conformity
6. Be listed in the Register of Certified Companies

Figure 16.2 Steps required for ISO certification. *Abbreviation*: ISO, International Standard Organization.

standards are the "ISO-9001" standards. It is these standards that can be applied to the health care industry and IVF in particular.

There are several steps for becoming ISO certified (Fig. 16.2). For any service company to become "ISO certified," it must first understand the standards that must be met. Typically, consultants with QMS experience work with the organization to understand and apply the standards. The time and expense for this process varies with the organization and its size but typically takes several months. The consultant must work with the employees to develop a QMS according to ISO standards. It must then be implemented to be sure it functions properly. A survey is conducted and, if successful, the certificate of conformity is issued.

The ISO standard is clearly laid out in a 23-page document of the elements required (Fig. 16.3). These requirements are readily available from the ISO organizations (http://www.asq.org/). These must be applied to the particular organization.

I have interpreted what ISO does for an organization to make it more understandable. A more detailed account can be found in the references at the end of the chapter. So, what does a QMS such as ISO teach us? Here are the main points: (*i*) documentation, (*ii*) a process approach, (*iii*) setting expectations for the staff, (*iv*) never be happy with the status quo, (*v*) leadership, (*vi*) communication, and (*vii*) focus on the customer.

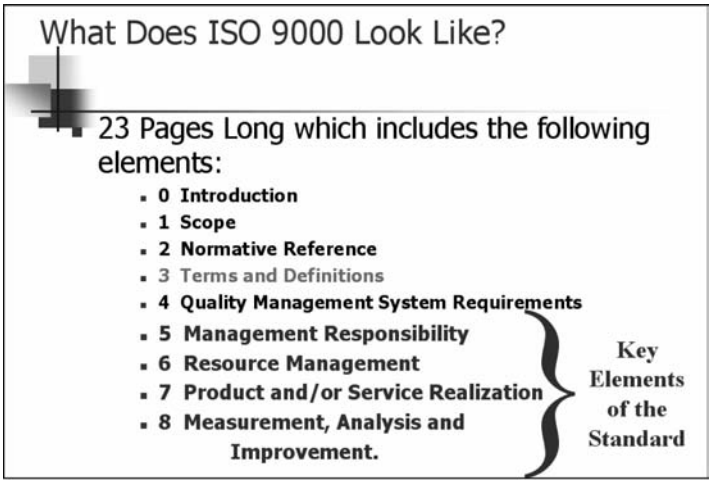

Figure 16.3 Elements required for ISO certification. *Abbreviation*: ISO, International Standard Organization.

Documentation

Before implementing a QMS at Boston IVF, we asked all employees to collect every single document that they have seen in the organization, no matter how old it was. These documents could include anything from the organization including protocols, handouts, marketing materials, etc. To my astonishment, we had close to 3000 documents at Boston IVF! Some were older versions of documents (e.g., consent forms), instructions that few people ever knew existed, etc.

A QMS requires a company to organize and maintain its documents. All documents need to be clearly identified and assigned to someone in the organization to control. All revisions made to any document must be authorized and recorded. All employees must know where to find the latest version of the document. It sounds simple but it requires considerable effort to identify which items are important and forces the organization to revamp and revise outdated materials. The exercise of identifying and managing organizations' documents is an important part of "cleaning house," resulting in a more organized and "neat" approach. Our company found it extremely useful.

Documentation goes beyond collecting and organizing materials. Virtually everything that goes on in an organization and involves a process should be written down. What should happen when a potential patient calls requesting information? How are patients' complaints handled? All these instructions should be clearly laid out.

A Process Approach to Problem Solving

So often in life and in business we make decisions based on emotions and not facts. A QMS should develop an organization's tools to solve problems based on the analysis of facts. Sure, gut feelings are often important, but both major and minor corporate decisions require careful analysis and process. For example, what happens if an employee has an idea for improving a procedure? He may tell his supervisor, but the idea could die if not carefully evaluated. There needs to be a method developed for suggestions to be heard and analyzed. This would be a process for improvement within the organization. Another simple example is ordering. Who can order what in the organization? What process exists for purchasing that covers all departments? All this must be documented and flow charts developed for certain processes so that all employees can clearly understand how things are done.

Setting Expectation for the Staff

It is typical for employees to want to succeed at their work. Human nature is to do a good job. Experience dictates that when employees are failing at their work, it is commonly the result of failure of the supervisors to clearly delineate the expectations, or the lack of training and tools that the employees receive.

It is vital that a clear job description and expectation be presented to the employee. Also, we often fall short of training staff on how to accomplish what we expect of them. And training does not start and end at the orientation. A QMS forces us to clearly identify how we manage staff training and competency. After all, a company's greatest asset is its employees, and it is imperative that performance is constantly measured and accountability delineated.

Never Be Happy with the Status Quo

A fundamental requirement of a QMS system is to foster continual improvement. There is a rare task in any organization that cannot be done better. So, how does one foster the notion that continual improvement is critical? This corporate personality trait starts from the top to the bottom of the company. Every employee with an idea for improvement must be encouraged to share their ideas and know the steps to take when presenting their suggestions. It is the employees on the front line who often know how to make their jobs more effective or efficient.

Leadership

The mission of any organization needs to be developed and followed. For that to occur, management must take leadership. Physicians receive no instruction in leadership training. In fact, I would say that it is uncommon for physicians who spend most of their career learning how to care for individual patients to also have the skills to motivate and lead an organization. These skills are typically developed in business (and not medical) schools. Typical fertility practices consist of several physicians practicing under one roof. A common frustration is bringing the group together to develop common practice patterns. It actually is not hard to accomplish this. But, there needs to be one person driving the process.

Books have been written on the skills required to be a leader. Some of these include, among others, good communication skills, belief in people, leading a balanced life, possessing a willingness to continually learn, and radiating positive energy. Leaders establish unity of purpose and direction. They create an environment where people are fully involved in achieving the organization's objectives. Every manager needs to lead their department, and a QMS focuses on responsibilities of management.

Communication

Proper communication both within the IVF center and with the outside world is of paramount importance. In fact, miscommunication can result in significant medical errors which are costly and can hurt the name of the IVF center. There must be an established method to handle patients' complaints or suggestions.

IVF centers involve many disciplines. A change in one area typically affects another. For example, if the physicians decide to order an extra three blood tests during an IVF cycle, then nursing, phlebotomy, billing, and other physicians must all be aware of the change. How do these changes in procedure get communicated and followed?

Physicians are often perceived as having their own way of doing things and unwilling to change to develop a more uniform method of treatment. This is not the case when physicians have a way to discuss and debate their views. There must be an effective process to discuss protocols through meetings and discussions. We find that retreats away from the office are the perfect venue to review clinical matters.

The key to delivering optimal service to our patients is effective communication. Do patients have trouble speaking to the nurse? Is voicemail preventing a patient from having the human touch? Frustration from inability of our patients to speak to the clinical staff in a timely manner is a frequently distressing issue for them.

Focus on the Customer

A QMS refocuses the organization on improving quality. But quality is not a vague concept or dream. If it cannot be measured, then it cannot be quality. The organization must be able to quantify and measure performance. Customer satisfaction is the tool that determines the ultimate success of an IVF center.

So, who are our customers? Certainly our patients are our primary customer. But for us to know if we are doing a good job, we must ask our patients how we are doing. Our product is

not babies, but rather the resolution of infertility. Some patients leave our IVF centers with a baby but are dissatisfied with their experience with us. Is that a success? And vice versa, we have many patients without success who are extremely appreciative of the efforts of our staff in helping them deal with and resolve their fertility issue. Our business is to provide a service, not a product. Since we cannot control whether the service will ultimately be successful in achieving a pregnancy, we must direct our efforts to helping our patients build their families by whichever means, or resolving their goals with comfort with child-free living.

We should not ask ourselves how we do at treating our patients; we must ask them. The best method is to survey them and follow the responses over time. Our surveys must be detailed enough to uncover deficiencies. All areas of the organization must be analyzed. Sometimes the results are surprising. How do doctors know that they are effective at what they do? Ask the customers and you will find out.

But an IVF center has many customers beyond the patients. We have relationships with pharmacies, pharmaceutical companies, vendors, and insurance companies. These companies are also our customers, and they must be managed as well.

Our employees are our internal customers. No company is effective with unhappy employees. The employees are one of the best marketing tools that a company has. These ambassadors must be satisfied to project the positive, excellent service provided.

RECOMMENDED READING

Alper MM, Brinsden P, Fischer R, et al. Is your IVF program good? Hum Reprod 2002; 17:8–10.

Carson B, Alper M, Keck C. Quality Management Systems for Assisted Reproductive Technology. London, UK: Taylor and Francis, 2004.

Keck C. Quality Management in Assisted Reproduction. Czech Republic: KAP CZ, 2003.

17 The true art: How to deliver the best patient care

Merle J Berger

I have practiced in the field of infertility for 40 years and have been a part of a medical specialty that has undergone dramatic transformation. When I first entered the field in 1970, eight years before the birth of Louise Brown, the first in vitro fertilization (IVF) success, the specialty was not practiced differently than any other medical specialty. The ratio of physicians to paramedical personnel was approximately 1:1.5, and the office facilities were little different from any other doctor's office. Finances were rarely an issue limiting care, and all surgeries were major procedures that were performed in a hospital.

Following the inception of IVF, the infertility practice has dramatically changed. Today, each one of our Boston IVF physicians needs approximately 10 paramedical people at their disposal in order to perform their specialty efficiently. Our facilities are in multiple locations, the largest of which encompasses almost 35,000 square feet of space including not only physician consultation and examination rooms, but administrator's space, laboratories, ultrasound rooms, hospital grade operating rooms, and even a complementary care center for acupuncture, massage, and counseling. With all these services in place, we can now offer a wide array of treatment options in a safe and efficient manner, but the inherent complexity in the discipline (and in the organization required to execute it) can appear emotionally and physically draining to many patients. While the infrastructure of an infertility practice has changed, the approach to caring for the patient has not. Over the years I have learned through trial and error the important ingredients to a successful infertility practice, which I wish to highlight in this chapter.

THE INITIAL ENCOUNTER

It all starts with the first encounter we have with the couple. After we have seen a new couple at the initial consultation, we just assume that they follow our instructions, complete the evaluation, return for a follow-up consultation, and then proceed with our recommended treatment. However, it is surprising with the successful treatment options that are currently available that many couples drop out and never return back to see us. For some it is based on the financial burden that is imposed, but this is not true for many others. Gleicher et al. reported that 36% of HMO-insured patients with full-scale infertility coverage in place discontinued care after six months following their initial presentation (1). Land et al. performed a retrospective study of their IVF population in the Netherlands where IVF is a covered treatment (2). They reported that almost half of patients voluntarily dropped out after three unsuccessful IVF cycles. These findings were also supported by a study out of Sweden that concluded that the dropout rate was 65% after three IVF cycles (3). The most frequent underlying cause of the dropouts was the psychological stress of the treatment. Thus, the challenge that we all face is how to keep our patients engaged in the process long enough so that they can benefit from the successful treatments we have to offer. We do this by minimizing the stress and inconvenience of the treatments, keeping them focused, and keeping tabs on how the patients are doing emotionally.

A STREAMLINED AND FOCUSED EVALUATION

In the past, couples would undergo an exhaustive and lengthy infertility evaluation that could last for months. The battery of diagnostic tests included multiple semen analyses, several blood tests, a hysterosalpingogram (HSG), BBT charts, endometrial biopsies, postcoital tests, various immune testing on cervical mucus and/or sperm, and a laparoscopy. Some of these procedures were not only painful and invasive but the results were often inconclusive, so they had to be repeated frequently, thus prolonging the time of the workup

and its associated discomforts and risks. Most of these tests are now considered unreliable and in retrospect do not often help the couple achieve their goal which, of course, is simply to have a healthy baby.

Today, the infertility evaluation is streamlined and encompasses only three basic tests: a cycle day 3 hormone assessment [follicle-stimulating hormone (FSH), estradiol (E2), thyroid-stimulating hormone (TSH), and prolactin], an HSG, and a semen analysis. All these tests can be completed within a month, so when the couple returns for a follow-up visit, a treatment plan can be devised and instituted rather quickly after initial presentation. With regard to each of these tests, the following should be noted.

Semen Analysis

There is no need to prescribe coital instructions or limitations such as abstinence prior to the test. Furthermore, if desired and if geography permits, the specimen can be produced at home in a sterile container rather than in the laboratory as long as it can be delivered within approximately one hour after it is produced. During cold weather, the sample should be kept at body temperature during transport.

Cycle Day 3 Hormone Studies

These studies can be obtained on either day 2 or day 4 of the cycle if day 3 is not convenient.

HSG

This procedure can be performed quickly and with minimal discomfort. It is best if this procedure is performed by someone experienced with a pelvic exam such as a gynecologist or a nurse practitioner. My approach is to use a Jarcho cannula so that I can avoid the application of a tenaculum or balloon. However, if a tenaculum is necessary to help reduce the discomfort, it should be applied slowly taking a minimal bite of the cervix. Try asking the patient to cough just as it is applied. To further reduce the discomfort with the examination I inject the contrast material "very slowly" and administer a NSAID one to two hours before the procedure.

TREATMENT

At the follow-up consultation, all the test results are discussed and I provide the couple with an overview of all treatment options, from the most conservative to the most aggressive. Often the options are quite clear. For example, in obvious male factor situations, the couple must choose between donor insemination and IVF/ICSI after an evaluation by a urologist. Similarly, everyone would recommend proceeding directly to IVF when the tubes are found to be occluded or if there is a history suggestive of adhesions. If the patient has an elevated day 3 FSH level, the couple must decide between a trial of IVF with the women's own eggs or to consider donor egg or adoption. If fibroids or polyps are present, the pros and cons of surgery must be discussed in detail.

From a practical standpoint, it turns out that many if not a majority of couples will be labeled "unexplained infertility" because the woman has regular ovulatory cycles and normal anatomy as determined by a normal HSG, and the male has a normal semen analysis. In the pre-IVF era, a laparoscopy would be done in such cases and endometriosis and/or adhesions would be discovered and treated in a large percentage of these couples. However, today we usually avoid laparoscopy unless the woman is symptomatic, so some causes of infertility go undiagnosed. Paradoxically, it is actually becoming simpler and more regimented to treat such couples. Until recently many of us would treat with multiple cycles of Clomid to superovulate the women with or without intrauterine insemination (IUI), proceed to approximately three cycles of gonadotropins with IUI, and then IVF as a last resort. In my practice, I have all but eliminated IUI treatment, since the evidence that IUI increases pregnancy rates when compared to having intercourse is quite weak. It is likely the hormones, not the IUI, to which we can attribute success. Naturally, when there are "mechanical" difficulties "delivering" sperm such as in patients with impotence, IUI is necessary. I have pretty much abandoned the use of gonadotropins and IUI, since the insurance companies in our state no longer require it for IVF approval. IVF is not that much more difficult, it is much more effective, and it better controls multiple pregnancies.

In the past, IVF was considered the treatment of last resort because it was thought to be painful, risky, and had very low success rates. Not only have success rates risen significantly but the process has evolved into a routine which is virtually painless, extremely safe, with much less disruption into the couple's lives. For instance, we no longer use any intramuscular injections; everything is given orally, vaginally, or subcutaneously. We minimize the number of visits required for monitoring and in some cases have minimized or even eliminated venipunctures, since there are several studies concluding that ultrasound monitoring alone does not impair outcome or place the patient at risk for ovarian hyperstimulation. After embryo transfer, the patients are encouraged to resume normal activities immediately including moderate exercise and intercourse. There is no evidence that a period of rest following the transfer improves outcomes, and it is our view that getting the patient back into their normal routine of life is advantageous. It is often reported that waiting for the pregnancy test is the most difficult part of the whole IVF process, so we provide them with a tip sheet which was prepared by our psychologist.

One of the most difficult clinical problems presents itself all too commonly in the couple with unexplained infertility in whom the women is 35 to 45 years old. Many of these women may have become infertile because they no longer have good eggs, but the day 3 FSH test has not yet risen. We are obliged to begin treatment without knowing whether there is any chance for success. Although, there are other methods to try and determine this such as AFC, AMH, and inhibin B, they are often normal as well or sometimes ambiguous. I have no doubt that in the future, we will have accurate methods to determine oocyte senescence and will be able to prevent patients from undergoing futile treatment.

PATIENT INTERACTION

Since most of our patients are under great stress during treatment, more contact seems better than less. After a patient begins a treatment program, there is a possibility that the physician may not see or speak to the patient directly for months at a time. The patients can feel abandoned by their physician even though the physician is supervising their care behind the scene, so it is best to see them during treatment or after the cycle is completed (whether pregnant or not), or at the very least speak to them by phone. Recently, I have been informing my patients that I am usually available by phone 7 days a week, 365 days a year (during the day), if they have difficult problems that the staff cannot deal with to their satisfaction. Most patients are enormously reassured when I present them with this information and rarely call.

Effective communication is the foundation of any successful organization, specially a medical practice. Communication needs to be prompt, accurate, and consistent. Everyone on the medical team needs to be on the same page. Trust can be eroded if the patient gets different answers to the same question posed to different team members. Unlike other medical practices, there is more frequent communication between the patient and the medical practice during a treatment cycle and there is always a sense of urgency of the communication. Therefore, one should stress to all the staff that all calls have to be answered by the end of the day and all issues must be resolved quickly. This is a challenge for our nurses who sometimes field 50 to 100 calls on a daily basis.

It is extremely important that we be honest with our patients about their chances of success, as infertility patients are desperate and vulnerable. It is important to respect the couples' wishes, but if the treatment is futile, it is time to stop it and move on to other options. For those who struggle with these recommendations, I often refer them to one of my colleagues for a second opinion and getting a counselor involved earlier rather than later can be a help.

IT IS A TEAM EFFORT

I have been blessed over the years with a highly successful practice in large part because of the excellent supportive staff I have had. The success of any infertility practice is dependent on the skill and quality of the staff including nurses, secretaries, sonographers, phlebotomists, counselors, and other ancillary staff. You may be the greatest doctor, but if you do not have a good staff to back you up, you are doomed to have difficulty. Each physician must recognize the importance of the team and must give each team member the respect they deserve.

DO NOT FORGET THE REFERRING PHYSICIAN

The lifeline for any specialty practice such as infertility is a constant stream of new patients being referred. While the referring physicians' goal is to have the patient return to their office pregnant (if they are obstetricians), they too need to be engaged in the process as well. I try to send frequent letters to referring physicians to keep them abreast of the progress. It does require time but these letters do not have to be elaborate—just a brief one is fine. If the patient needs a basic surgical procedure (i.e., D&E, laparoscopy, hysteroscopy), we often ask the gynecologists to see if they are interested in performing it.

SUMMARY

Because of the nature of our specialty, the patients must relate not only to their physicians and nurses, but to laboratory personnel, technicians, and even insurance and financial personnel. The patients must be treated as customers but not made to feel like customers, so it is incumbent upon physicians who manage practices to learn skills never imagined in medical school, residency, or fellowship. With all this in mind and incorporating some or all of the suggestions described above, the patients' acceptance rates can only improve, which ultimately increases the chances of success as well as the popularity of the providers.

REFERENCES

1. Gleicher N, Vanderlaan B, Karande V, et al. Infertility treatment dropout and insurance coverage. Obstet Gynecol 1996; 88:289–293.
2. Land JA, Courtar DA, Evers JL. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. Fertil Steril 1997; 68:278–281.
3. Olivius K, Friden B, Lundin K, et al. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2002; 77:505–510.

18 Medical ethics in reproductive medicine

Steven R Bayer and Kim L Thornton

The introduction of in vitro fertilization (IVF) over 30 years ago is one of the most significant advancements in the field of reproductive medicine. Over 3 million babies have been born worldwide as a result of this technology. IVF has benefited many infertile couples, but has also resulted in the emergence of ethical dilemmas that continue to challenge IVF centers today. The specialty is ethically charged to begin with, since its primary focus is on reproduction. Even though the concept of reproduction means something different to all of us, the ultimate goal of reproduction is to produce and nurture one's offspring. While this is not refuted, societal concerns are the means that may be undertaken to produce this offspring. In the traditional sense, the act of reproduction is a private, natural, and conjugal act between two people. However, treatment with the available technologies does everything but meet these criteria. Nevertheless, the right to procreate or reproduce is a liberty that is held sacred by all of us. As caregivers, we must respect this right, yet at same time it is our responsibility to use the available technologies in a responsible manner. This is the role of ethics in reproductive medicine.

DEFINITION

Ethics is defined as a code of moral principles derived from a system of values and beliefs that helps define the correctness of our actions.

ETHICS IN MEDICINE AND NURSING

The practice of medicine and nursing is founded on ethics. Physicians take the Hippocratic Oath, where it is stated, "... I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous." A similar statement is present in the nursing code of ethics, The Nightingale Pledge, "... I will abstain from whatever is deleterious and mischievous and will not take or knowingly administer any harmful drug." In society, it is implicit and expected that physicians and nurses practice ethically within the bounds of their profession and always do what is in the best interest of their patients. This is understood, but whose interests do we need to protect? It is complicated in the field of reproductive medicine considering that there can be many participants involved in the treatment. Obviously, we have to look out for the interests of the woman undergoing treatment who is assuming the immediate risks of the treatment and the risks associated with the pregnancy. We also have to protect the rights of her partner who is not exposed to any risks of the treatment but this individual must first desire to become a parent and also be willing to care for any offspring(s) that result from the treatment. As providers, we must also determine the impact of our decisions on the yet unborn child. To further complicate matters, there are other participants to be considered in cases of egg donation and gestational surrogacy. Therefore, before any treatment is started it is imperative that *all* participants are adequately informed and closely evaluated to ensure that their interests are not compromised as a result of the treatment.

INTEGRATION OF ETHICS INTO CLINICAL PRACTICE

In every center, there should be an opportunity to deal with ethical issues concerning the patient care that is provided. To this end, there are four key components that must be in place, including open dialogue, an ethics committee, available resources, and ethical analysis.

Open Dialogue

When compared to most other medical problems, the treatment of the infertile couple is unique because it can only be accomplished through the coordinated effort of a team made up of physicians, nurses, scientists, mental health professionals, and other key personnel. Every

member of the team deserves equal respect considering each plays an important role in the treatment of the couple. Each team member interacts with the couple at a different level, which gives each a unique perspective regarding the treatment that is being rendered. Each member must feel comfortable with the treatment that is being performed, otherwise they must be able to voice their concern freely and it must be taken seriously.

Ethics Committee

Every center should have a committee in place and a forum to discuss ethical issues. The committee can simply include a physician, nurse, mental health professional, and a representative from the laboratory. Depending on the topic that is being discussed, input from an ethicist, lawyer, or member of the clergy may also be helpful. While it is optimal to have periodic committee meetings, it may be necessary to assemble the committee on short notice to resolve an urgent issue. One role of the committee is to review the ethical issues concerning a specific treatment (i.e., egg donation, gestational carrier treatment). If a decision is made to offer the treatment, the next step is to develop a comprehensive policy detailing how the treatment will be administered. A final role of the committee is to discuss ethical issues concerning individual cases.

Available Resources

An important part of an ethical analysis is utilization of available resources. The resources come from the knowledge of individual committee members and from outside resources, as well. The Ethics Committee of the American Society of Reproductive Medicine (ASRM) was formed in the mid 1980s and has been proactive in addressing ethical issues. They have published reports and statements titled "Ethical Considerations of Assisted Reproductive Technologies" as supplements to the journal *Fertility and Sterility*. The largest compilations of position papers of the ethics committee were published in 1994 and 1997, and cover over 20 different topics, but the ASRM has published position papers on other various topics as new ethical issues have arisen. These position papers and statements are available online (http://www.asrm.org).

A sampling of positions published in the past few years are as follows:

- Access to fertility treatment by gays, lesbians, and unmarried persons
- ASRM: Defining embryo donation
- Fertility preservation and reproduction in cancer patients
- Fertility treatment when the prognosis is very poor or futile
- Child-rearing ability and the provision of fertility services
- Informing offspring of their conception by gamete donation
- Family members as gamete donors and surrogates
- Donating spare embryos for embryonic stem-cell research
- Human immunodeficiency virus and infertility treatment
- Preconception gender selection for nonmedical reasons
- Financial incentives in recruitment of oocyte donors

The Ethical Analysis

The framework that is used to perform an ethical analysis is based on several fundamental ethical principles. These principles are used when performing a formal ethical analysis and used by the physician in day-to-day patient care. Before an ethical analysis can be performed, one must first have underlying values and the proper perspective. John Gregory (1724–1773) was instrumental in advancing the concept of medical ethics through his invention of "*professionalism*," which changed the focus of medical ethics from being physician-based to patient-based. He described virtues that a physician must exhibit to provide ethical care of patients. Others including Thomas Percival (1740–1804) expanded Gregory's professional virtues. While these virtues apply to the physician-patient relationship, they are also applicable to all of those who participate in an ethical analysis.

- **Integrity:** a commitment to the practice of medicine in accordance with the standards of intellectual and moral excellence.
- **Compassion:** sympathetic awareness of a patient's distress along with a desire to diminish the distress.
- **Self-effacement:** putting aside and not acting on irrelevant differences between oneself and the patient (i.e., religion, race, sexual orientation, socioeconomic status, etc.).
- **Self-sacrifice:** the sacrifice of one's interests to protect and promote the interests of others.

Therefore, an ethical analysis must be done with compassion, integrity, and devoid of any bias or prejudice. The important ethical principles and concepts that are used to perform an ethical analysis are discussed below.

Principle of Respect for Patient Autonomy

Patient autonomy is one of the most powerful and prevailing ethical principles. Autonomy is synonymous with independence or freedom. This ethical principle implies that it is the right of the patient to choose his/her treatment and that this choice must be respected. However, it is the obligation of the physician to truthfully inform the patient of the consequences of any action including the benefits, risks, complications, and alternatives. This principle is founded on the concept of informed consent.

The Principle of Double Effect

The principle of *double effect* is in essence a compromise of two other important ethical principles: *beneficence* and *nonmaleficence*. The principle of beneficence is the driving force of patient care. This principle refers to the ultimate goal of any treatment, which is to do something good for the patient. The principle of nonmaleficence is to do no harm to the patient. Should we strictly adhere to the nonmaleficence principle, then no treatment would be offered to our patients because there is always the possibility of a bad outcome. The decision to move forward with a treatment occurs when there is a greater balance between good and bad outcomes. While it is important that the harm or risk of any treatment be recognized, the absolute avoidance of harm should not take more importance over the potential benefit of any treatment.

Principle of Distributive Justice/Public Stewardship

The principle of justice mandates fair and equitable treatment for all. Society has a responsibility to adhere to this principle that is in accordance with support of human dignity and human rights. Therefore, there should be no prejudice in the administration of treatment to the populace and equal access for all. It also applies to the individual physician as well; the physician should not in any way be prejudicial in regard to who is offered treatment and who is not.

Paternalism

Paternalism refers to the action of a physician who in an authoritative and directive fashion influences the decision-making process. If this action is based on clinical knowledge and absent of any bias or prejudice, it is consistent with the principle of double effect, but at the same time it counters patient autonomy. As fertility specialists, we feel obligated to carry out our patient's request; however, in some circumstances, an alternative treatment or no treatment at all may be the indicated course of action.

Standard of Care

When examining any therapy, it is important to determine whether this treatment falls within the standard of care for the community. The community may be as broad as the national

ASRM or narrower as the city where the practice is located. This may hold special importance if this treatment has never been offered—a situation where more critical assessment of all potential outcomes should be discussed before the treatment is offered. However, even if a treatment falls into the standard of care, it does not necessarily mean that it is guaranteed to be safe. An example of this is the complications following the administration of diethylstilbestrol (DES) to pregnant women in the 1960s.

Impact on the Community

While any treatment may be ethically sound, it is important to step back and assess the impact of its potential effect on the community. Again, the definition of community can vary. A narrow definition of community can be the IVF center itself. Within any center, there may be staff members who have strong opinions for or against a proposed treatment. For instance, after careful analysis and deliberation, it may be determined that gender selection is ethical. However, if team members are uncomfortable with this procedure, then there should be reconsideration whether to offer gender selection at all or only offer it under certain conditions. A broader definition of community can be society at large. The pursuit of human cloning by a small group of scientists several years ago drew worldwide attention. There was public outcry that cloning crosses ethical boundaries and some countries enacted laws against this practice.

Case Presentations

Case 1

A 35-year-old G0 P0 female presents with a history of infertility. During the workup, it was determined that both she and her husband were carriers of cystic fibrosis (CF)[a]. The couple was seen in consultation and they were informed that they had a one in four chance of having a child that would be affected by the disease. Alternatives were discussed including IVF/preimplantation genetic diagnosis (PGD), genetic testing after pregnancy was established, and donor gametes. The couple could not afford IVF and basically was not overly concerned about having a child with the disease in part because they had a friend who had a three-year-old daughter with CF and "she was *doing just fine*." To provide further counseling, the couple was referred to a cystic fibrosis specialist at a local children's hospital. The couple was seen in follow-up and further discussions ensued. Their desire was to start treatment with intrauterine inseminations. Prenatal genetic testing was again discussed but the patient was uncertain if she could undergo a termination of the pregnancy. At this point, it was concluded that the couple had been adequately informed and treatment was offered.

This case highlights the important ethical principle of respect for patient autonomy which is founded on informed consent. While it may have been the right decision to offer treatment in this case, if the female and male were carriers of a more severe or fatal disease (i.e., Tay–Sachs disease, Fanconi's anemia, etc.) that would cause severe suffering to an offspring, then the right decision may have been not to offer treatment.

Case 2

A 40-year-old G1 P0010 woman presents with a five-year history of unexplained infertility. She was diagnosed with cerebral palsy at birth and is a paraplegic confined to a wheelchair. She had medical problems including hypertension and obesity. At another center, she underwent treatment with clomiphene citrate plus intrauterine inseminations, which were unsuccessful. She now presents for consideration of more aggressive treatment. Because of her medical state, she was sent to a high-risk obstetrician for counseling about the risks and complications associated with a future pregnancy. There was added concern that the treatment may result in a multiple pregnancy that could further heighten any risks. She was given medical clearance to proceed. During the workup, a hysterosalpingogram confirmed the presence of multiple filling defects in the uterine cavity. A decision was made to proceed with a hysteroscopy. The

[a]Cystic fibrosis is one of the most commonly inherited diseases in the Caucasian population. It results in thickened mucus production that can alter pulmonary and pancreatic function. The median life expectancy of affected individuals is 37 years.

preoperative cardiac evaluation by the anesthesiologist confirmed that she had pulmonary hypertension. During pregnancy, pulmonary hypertension results in a 50% rate of maternal mortality. The patient was seen in consult and the implications of her condition were discussed. However, she was not concerned and stated that "I am a survivor and always beat the odds." She wanted to move forward with the surgery and then ultimately treatment. A decision was made by the physician not to treat this patient based on medical reasons and the high likelihood of a bad outcome during a future pregnancy—*maternal death*.

This case illustrates an example of paternalism and how it influenced the decision not to move forward. The decision not to treat this patient was done in an unbiased fashion and was based on medical fact. It was determined that the severity of a bad outcome as a result of the treatment far outweighed the benefit of the treatment—the principle of double effect. The decision not to treat countered patient autonomy.

Case 3

A 40-year-old G1 P1 woman presents with her husband with unexplained infertility. The couple has one daughter and they inquired about gender selection in their quest for a male offspring. They were told that it is the policy of the center that gender selection can only be done when there is another indication to do preimplantation genetic screening (PGS). In addition, a visit with a social worker is mandatory and the couple had to agree to transfer embryos of the undesired gender if they were the only ones available. The topic was never brought up again by the couple and they underwent several cycles of insemination treatments that were unsuccessful. They then pursued IVF treatment and requested that, because of the woman's age, they would like to have PGS performed to rule out aneuploidy. The couple underwent their first cycle of treatment. Eight embryos were biopsied and only two were found to be normal. The couple presented for the embryo transfer; when they found out that both embryos were female, they chose to forego the transfer and discard the embryos. During the follow-up visit, the couple was informed about the center's policy regarding gender selection. They never returned for another cycle.

Comment: A couple's desire for an offspring of a certain sex has been present since antiquity and for most it is for family-balancing purposes. There has been speculation that a woman's diet or the frequency or timing of intercourse can impact on whether she has a male or female infant. Over a decade ago, sperm-washing techniques were developed to select out the X or Y bearing sperm. In retrospect, all of these techniques did little to help the couple achieve their goal. The advances in IVF and PGS have provided the opportunity to determine the gender of embryos. However, there is ongoing debate as to whether gender selection is an ethical practice. At one end of the spectrum is the couple who presents stating that they have three sons at home and would like to have a female offspring balancing the family. They would also transfer embryos of the undesired gender if they were the only ones available. This is a situation that many would agree is an acceptable one to consider gender selection. At the other extreme is the couple who request gender selection for their first born and also indicate that if the PGS testing demonstrates no embryos of the desired gender, under no circumstances would they consider transferring embryos of the undesired gender. Moreover, if they conceive after transfer of an embryo and the PGS test happened to be incorrect, they indicate that they would terminate the pregnancy. This is obviously a situation where many clinicians would feel uncomfortable in proceeding with the request.

At Boston IVF, there has been an evolution in our approach to gender selection over the past decade. Initially we were concerned about whether offering gender selection was an ethical practice and we elected not to offer this option to couples. Over time, the clinicians, nurses, and embryologists in the laboratory handling these embryos became more comfortable with the concept of gender selection for family-balancing purposes for the infertile couple who was undergoing IVF plus PGS for aneuploidy screening. Further, if only embryos of the undesired sex were available, then it was requested that the couple agree to transfer them. Presently, we have modified the policy once again such that any couple (fertile or infertile) can undergo gender selection for the purposes of family balancing or for their first born. In addition, the disposition of embryos of the undesired gender will be left up to the couple. This policy was developed by a subcommittee who reviewed position papers written by the ASRM on gender selection. After the policy was developed, it was presented and approved by the laboratory, nursing, and

medical staff at Boston IVF. An important part of the written policy is that all couples desiring gender selection must meet with a social worker. After this visit, the social worker and treating physician review the case and make a determination as to whether it is appropriate to move forward with the treatment.

Case 4

A 46-year-old G0 P0 woman presents with a history of infertility and a desire to proceed with IVF treatment. She has regular menstrual cycles and is in good health. The clomiphene citrate challenge test was normal. The physician had a long discussion about the impact of age on infertility and treatment success. The chance of an IVF cycle being successful in a woman of this age is 0% to 1%. Other treatment options were discussed with the couple including egg donation and adoption. The couple was adamant that they wanted to proceed with the treatment. The physician did not give in to their wishes and they left for a second opinion.

One of the important ethical principles is beneficence. The chance of pregnancy following treatment in this case was essentially zero. The risks of IVF treatment are relatively low, however, in this particular case the risks outweighed the benefit and the decision was made not to allow this couple to pursue treatment. In this case, the clinician exercised the right to decline to treat the couple on the basis of their estimate of the futility of treatment and followed well-developed guidelines established by the practice. One might argue that, in this situation where there are conflicting interests between the clinician and the patient, the conflict may be managed differently. The Ethics Committee of the ASRM published a position paper addressing the role of treatment in the infertile patient when the prognosis is considered very poor or futile.[b] *The committee defined a very poor and futile prognosis when the anticipated success rate is 1% to 5% and <1%, respectively. They concluded that the physician has the right to refuse to initiate treatment in these cases; however, treatment may be considered when it is determined that the couple would receive a psychological benefit. Before the treatment is pursued, the couple must be thoroughly counseled as to the low odds of success, and they should meet with a mental health professional.*

Case 5

A 56-year-old woman presents with her husband for consideration of egg donation. Their 18-year-old daughter, their only child, recently died from complications of leukemia. She has been menopausal for five years. She is in excellent health and was recently provided medical clearance from her internist to proceed with egg donation and an eventual pregnancy. The reproductive endocrinologist referred to the center's policy that the upper age limit for egg donation was 50 and therefore the patient could not undergo the treatment. After continued discussion, it was clear that the couple was still grieving the loss of their daughter. They were referred to a social worker for grief counseling. Following the counseling session, the couple decided not to pursue treatment.

Comment: The well-publicized stories of older women, including the 70-year-old woman, who achieved pregnancy following egg donation give many a level of discomfort. Should there be an upper age limit for egg donation? There are medical concerns about the documented increased risks of pregnancy in older women. There are also ethical concerns for children being born to older women. An untimely death of the mother could place the potential offspring in jeopardy.

Boston IVF developed a policy setting the age limit at 50 for women undergoing egg donation. This decision was based on the documented medical risks to the older woman during pregnancy and ethical concerns for the unborn child. It was also determined to be the standard in the community after other IVF centers in the Boston area were polled.

Case 6

An unmarried, female, same-sex couple presented for consideration of treatment. Their desire was that one partner would donate eggs to the other partner and a known sperm donor would

[b]Fertility treatment when the prognosis is very poor or futile. Fertil Steril 2009; 92:1194–1197.

be used. At Boston IVF this treatment is termed "Partner-Assisted Reproduction (PAR)." The first woman is a 35-year-old G1 P1 female in good health and meets all criteria to be an egg donor, and the recipient is 43-year-old G0 P0 female who is also a suitable recipient. Therapeutic donor insemination was offered to the latter patient but there was concern that her advanced age would significantly decrease the chance of success. The couple was offered PAR treatment and the recipient conceived after the first cycle of IVF treatment.

In simple terms, this case involves a woman who achieved pregnancy following known egg and known sperm donation. ASRM guidelines were used to determine the suitability of both the egg and sperm donor. It is also important to explore anticipated roles and responsibilities of each participant in the upbringing of a future offspring. Therefore, all parties met with a social worker and a lawyer. As a result of the legal counseling, a contract was developed and signed by all participants detailing their rights and any responsibilities.

Staying Out of Trouble

Dealing with ethical issues involving individual patients can be time consuming and stressful. Being proactive will help avert some of the ethical dilemmas. Some tips are as follows.

Written Policies and Procedures

It is important to have written policies and procedures in place for the treatments that are offered. These written documents should be developed by the team and represent a consensus of the group. These guidelines should be reviewed and updated on a regular basis. It is important that patients are made aware of specific criteria elaborated in these policies that impact on their care. Individual cases that fall outside the guidelines can be reviewed by the treatment team.

Stop Them at the Gate

When an ethical issue involving a couple is encountered, it is of paramount importance that treatment is not initiated until the issue has been thoroughly investigated and resolved. If treatment has been started, it is much more difficult to halt the treatment if it is deemed necessary, and from the patient's perspective, the physician has already given approval for the patient to undergo treatment. As physicians, we want to please our patients but in some situations the issue of concern must be investigated before proceeding.

Don't Be the First

The field of reproductive medicine is a highly competitive field and there is motivation to set yourself apart from competitors by offering a new treatment modality. In some cases, it may be better to be cautious and not offer the treatment until it has been accepted and all of the issues have been worked out. However, in some cases it may be worthwhile to proceed as long as all of the potential implications of the treatment have been researched and discussed.

Get Legal Input

Don't be shy requesting legal input. There are lawyers who are well versed in reproductive law and are also helpful in the development of consent forms.

Take a Stand

As physicians, we have the right to refuse treatment in situations where we feel uncomfortable or where there is concern about the consequences of treatment. In these situations, it is important that the physician maintain the high ground and do what is right. When discharging a patient from a practice, it is important not to abandon the patient. An appropriate level of care must be provided that falls within the guidelines of the practice for a certain period of time, which allows the patient to establish care with another provider.

19 The mind/body connection

Alice D Domar

INTRODUCTION

Every woman who is experiencing infertility has been told at some point to "just relax," "go on vacation," "quit your job," "stop trying so hard," or the old favorite, "just adopt and then it will happen." The assumption behind all of these comments is that the woman's stress level is in some way preventing conception. But is that true? Are infertile women more stressed than fertile women? And if so, does their stress level preclude pregnancy? Can it truly prevent infertile women from benefiting from the advances in reproductive technologies? And will relaxing indeed lead to conception? These are the questions which are answered in the following pages.

THE PSYCHOLOGICAL IMPACT OF INFERTILITY

One of the problems with assessing the distress levels of infertile women, or many other kinds of patients facing medical treatment for that matter, is that the typical way to assess distress is with self-report psychological questionnaires. And in order to get accurate data, one needs to collect accurate responses. However, many patients feel an intense need to come across as a "good patient," and may thus underestimate their level of distress. This phenomenon was highlighted in a recent study in Sweden on in vitro fertilization (IVF) patients (1). Women were psychologically assessed several times during an IVF cycle and their well-being scores were in the normal range and consistently comparable with Swedish reference values. The authors theorized that the reason why patients tested so well is that they "kept their worries and anxieties to themselves because they had great expectations regarding both themselves and the anticipated treatment. Perhaps they also wanted to show how well they felt and that they could handle the treatment." Several other studies with infertility patients have come to similar conclusions; self-report measures in the infertile population may well underestimate the level of distress.

Despite this concern, there have been numerous studies using self-report measures that have shown that infertile women have more symptoms of depression and anxiety than the general population. Research has shown that the prevalence of depressive symptoms in the infertile population is twice that in the general population (2). In addition, infertile women have comparable levels of anxiety and depression as women with heart disease, HIV+ status, or metastatic cancer (3).

However, the gold standard in psychological testing is not a self-report measure but instead a structured psychiatric interview. A recent study on 112 patients presenting to an infertility clinic for the first time included such an interview (4). A total of 40.2% of the women met the criteria for a psychiatric disorder; the most common was anxiety disorder (23.2%), followed by depressive disorder (17%). This compares with a community sample prevalence of 3%.

It is obvious that infertile women are suffering. If almost half of new infertility patients report significant psychological symptoms, since the level of distress tends to rise as duration increases, and to intensify as treatment becomes more complex, it is reasonable to theorize that more than half of patients actively receiving treatment are experiencing a diagnosable level of anxiety and/or depression.

There are many reasons why infertile women experience such high levels of distress—the process impacts their relationship with their partner, their sex life, their relationships with family and friends, their job, their financial security, and their relationship with God. Men and women do not react to infertility in the same way, at the same time, or with the same level of commitment. In most cases, the infertile couple is surrounded by the fertility of their siblings, friends, neighbors, and coworkers. Imagine the couple who start trying the same time as a sibling or close friend, then find themselves two or three years later still childless, while the

other couple announces their second pregnancy. Many jobs involve structured meetings and travel, neither of which is conducive to invasive and unexpected infertility treatments. Money is already an issue for most couples; the thought of spending $12,000 on a treatment that has less than a 40% chance of success forces many couples into conflict. Finally, the issue of religiosity needs to be addressed. The majority of individuals in this country pray and believe in a higher power. For many, this is the first time that God has not answered their prayers, leading many to question either their own level of goodness, or the existence of God.

Whether a particular couple experiences conflict in one of these areas or more likely in all seven, it is not surprising that infertility can cause such emotional upheaval. To top it off, the comments from well-meaning family and friends, such as the ones that introduced this chapter, can contribute to a blame-the-victim mentality.

THE IMPACT OF STRESS ON TREATMENT OUTCOME

Since IVF involves a relatively similar protocol throughout the world, research on the impact of stress on reproductive outcome has focused mainly on IVF patients. There have been at least 26 studies that have investigated the relationship between stress prior to or during an IVF cycle and subsequent pregnancy rates (5). The vast majority of these studies show a significant relationship between distress and pregnancy (i.e., the most distressed patients have the lowest pregnancy rates), several studies found a trend in that direction, and five did not find any relationship. It is possible that there may be cultural issues that are contributing to the conflicting results. For example, a large study from the Netherlands (6) did not find a relationship between distress and IVF outcome but the authors noted that there was a floor effect—few of the patients in the study reported any distress at all. It is apparently common in some cultures to underreport distress on self-report scales.

Perhaps the best-designed study was one on 151 women prior to beginning an IVF or GIFT cycle (7,8). The strength of this study was the fact that they collected numerous psychological factors, including not only how stressed the patients reported feeling, but what factors about the treatment were the most stressful, as well as a number of physical factors, such as number and quality of oocytes retrieved, pregnancy outcomes, and birth weight. The baseline level of stress was significantly related to outcome; stress levels were correlated to number of retrieved oocytes, percentage fertilized, pregnancy rates, live birth rate, and birth weight. The strength of the correlation between distress and pregnancy was strong—the subjects who expressed the least baseline level of distress were 93% more likely to give birth than the patients who reported the most baseline level of distress.

The majority of research to date supports the hypothesis that stress hampers the effectiveness of reproductive technologies (9). The mechanism of action however is unknown.

THE IMPACT OF PSYCHOLOGICAL DISTRESS ON DROPOUT RATES

Until recently, it was assumed that patients would pursue infertility treatment until one of two events occurred—their physician told them that further treatment was unadvisable (so-called active censoring) or they ran out of money. This theory was well accepted by most health care professionals in the infertility field, simply because the patients they saw on a day-to-day basis were the ones who chose to continue treatment. The ones who dropped out of treatment came to no one's attention and were thus forgotten. However, research conducted in the past few years reveals a completely different scenario—patients drop out in large numbers. And since the new research is coming from countries where IVF is covered by insurance, money was clearly not the motivation to terminate treatment. Anywhere from 40% to 65% of insurance-covered nonpregnant patients discontinue treatment prior to completing their covered cycles.

As it turns out, active censoring is relatively rare; a study from the Netherlands, in which there was a cumulative dropout rate of 62% after three cycles, found that only 14% of the patients who dropped out of treatment did so because of physician recommendation (10). The most recent research shows that the primary reason why patients drop out of IVF treatment is psychological stress. In a Swedish study of 974 couples, the patients reported that "psychological burden" was the reason they discontinued treatment (11). An Australian study showed the same results—66% of couples who dropped out of IVF cited the emotional strain as their reason for terminating treatment (12). In a study of 211 couples who dropped out

for reasons other than active censoring, the most commonly cited reason was psychological burden, followed by the perception of a poor prognosis (13). This study also revealed that the couples who dropped out of treatment were as satisfied with their care as couples who remained in treatment, so the quality of care does seem to be a contributing factor in patients' stress levels.

In a recent study on insured couples in the United States (14), stress was once again the most common reason cited in couples who dropped out of treatment. In addition, age was a factor in terms of dropout behavior; 34% of women aged 40 and below who were insured for six IVF cycles did not begin a third cycle, while for women aged 40 to 42, the percentage of those who dropped out was 68%.

Obviously, couples who drop out of treatment are likely to sacrifice their chance of pregnancy. A retrospective German study on 2130 IVF patients analyzed the cumulative pregnancy rate and found that 31.4% of couples achieved pregnancy after three cycles; however, if couples had undergone one more cycle, the rate would have increased to 41% (15). If a couple had undergone the six insurance-covered cycles, the rate would have climbed to 60%.

Finally, it appears to be possible to predict which patients are more likely to drop out of treatment. In a prospective study of women beginning IVF, it was determined that pretreatment levels of depression were significantly predictive of patient treatment termination after only one cycle (16).

Two recent studies indicate that the impact that stress can have on treatment retention is actually determined prior to even seeking medical intervention. In a study of couples in California who did not pursue any treatment after an initial consultation (17), it was discovered that depressive symptoms played an important role; depressed women were less likely to pursue treatment. An Australian study noted that women who reported depressive symptoms were unlikely to have sought out medical advice for the treatment of their infertility (18).

Thus, it is obvious that psychological distress plays a large role in IVF retention. Patients who are depressed prior to treatment are more likely to drop out after only one cycle and throughout the IVF process, patients cite psychological burden as the primary reason for dropping out of treatment. Obviously, premature termination limits a couple's ability to get pregnant. What is not known, however, is if it is possible to psychologically intervene with distressed patients, in order to support them to continue treatment or even to initiate it.

THE IMPACT OF PSYCHOLOGICAL INTERVENTIONS ON INFERTILE WOMEN

If one accepts the theory that distress is associated with lower pregnancy rates in infertile women, then interventions designed to decrease distress should lead to higher pregnancy rates. And, in fact, the majority of the research to date supports this notion. Although there are only a handful of randomized, controlled prospective studies, most do indeed show a positive effect from psychological interventions. In a meta-analysis of the literature (9), the authors concluded that group as well as individual and couples psychotherapy is associated with the alleviation of anxiety and depressive symptoms. In addition, the meta-analysis also indicated evidence for the enhancement of conception rates through psychological therapy.

Psychological interventions can take many forms, ranging from individual therapy to stress-management programs. The term "counseling" can take many forms. Most would assume that would involve treatment for an individual or couple. But counseling can apply to many forms of intervention. For example, a randomized, controlled, prospective study was performed on 60 IVF patients in Turkey to assess the impact of counseling on IVF patients (19). In this case, counseling was provided by the IVF nurses and included several hours of personal attention and support. The couples who received this intervention reported lower anxiety and depression scores as well as a 43% pregnancy rate, compared to a 17% rate in the control group who received routine nursing care.

There has not been solid data to support the use of brief psychotherapy with infertile individuals or couples. And, in fact, the most recent research does not show any benefit (20). In a study of 265 couples in the Netherlands, 84 of the couples agreed to be randomized to either a routine care control group or to an intervention which included three sessions with a social

worker. There were no differences in psychological parameters or pregnancy rates between the two groups. This is the most recent of several studies which have not shown any definitive benefit of brief counseling.

Research on other interventions has shown more promise. In one randomized, controlled, prospective study, 185 infertile women were assigned to either the 10-session Mind/Body Program for Infertility, or a 10-session support group, or a routine care control group (21). The mind/body intervention included instruction in relaxation techniques, stress management strategies, and lifestyle modifications. The support group included time for members both to voice their concerns about the impact that infertility was having on their lives as well as to provide support to each other. All subjects continued to receive routine infertility care. During the one-year follow-up study period, 55% of the mind/body patients and 54% of the support group patients experienced a live birth, compared to only 20% of the control subjects. In addition, there were differences in psychological health (22). The mind/body patients experienced a decrease in negative symptoms such as anxiety and depression, the support patients remained the same, while the control patients experienced a worsening of symptoms.

In a subsequent study in Japan, 74 subjects were randomized to either a five-session mind/body group or a routine care control group (23). The mind/body subjects experienced a significant decrease in psychological distress and natural killer cell activity while the control subjects experienced no change. In addition, 38% of the mind/body subjects became pregnant during the study period compared to 13.5% of the control subjects.

In the most recent research performed at Boston IVF (24), 97 women who were about to begin their first IVF cycle were randomized to either attend the 10-session mind/body program or to a control group. Only 9% of the mind/body patients were able to start the program prior to their first IVF cycle but 79% were able to prior to their second cycle. Clinical pregnancy rates for cycle 1 were 43% for both groups but for cycle 2, they were 52% for the mind/body patients and 20% for the controls.

The data thus far on the effectiveness of psychological interventions points to a longer-term stress-management kind of approach, rather than the more traditional use of individual or couples' counseling or brief therapy. There have been two meta-analyses on psychological interventions. One (25) concluded that skill-based interventions were more effective than more traditional therapy, and the other (26) concluded that interventions of at least six sessions are more effective than shorter ones.

Mind/body interventions have been well researched; their effectiveness has been established with a variety of medical and psychological conditions, including hypertension, menopausal symptoms, premenstrual symptoms, insomnia, chronic pain, anxiety, cardiac arrhythmias, chemotherapy side effects, depressive symptoms, and gastrointestinal problems. The application of mind/body techniques to infertility began in 1986 and the clinical use is increasingly rapidly.

THE MIND/BODY PROGRAM FOR INFERTILITY

I was part of the first mind/body infertility program that opened in 1987 and was designed to teach relaxation and cognitive strategies to infertile women. The goal of the program was psychological symptom reduction, not pregnancy, and this message was disseminated to all interested patients. After the first 50 women completed the program, it was noted that they were experiencing significant psychological symptom reduction as well as a higher-than-anticipated pregnancy rate (27).

At this point in time, after 18 years of clinical practice, pregnancy rates within six months of program completion average 45% to 50% and every psychological parameter measured, including anxiety, depression, hostility, and confusion, decrease significantly. In addition, patients report significant reductions in physical symptoms, such as insomnia, headaches, abdominal pain, and gastrointestinal symptoms. Health care professionals from around the world have been trained as group leaders and uniformly report the same positive changes.

All potential participants must attend an intake appointment with the group leader. They are mailed a long questionnaire that they are instructed to bring to the intake. There are multiple goals for this session. It provides an opportunity for the two of them to get to know

each other better, the group leader obtains a comprehensive medical, psychological, social, and lifestyle history, the group leader can explain how the program is run, and it gives the patient an opportunity to ask questions.

Groups are normally led by a mental health professional with extensive knowledge of infertility. Each group leader is supported by two "peer counselors" who are graduates of the program; peer counselors are chosen because, as program participants, they experienced excellent symptom relief and successfully incorporated the mind/body skills into their lives. They serve as role models as well as being a liaison between the leader and the patients. The mind/body program also includes a buddy system. Patients are paired with another patient the first night. If there are two patients with similar circumstances (for example secondary infertility, recurrent miscarriages, or a history of a stillbirth), they are paired up; otherwise it is done on a geographical basis. Buddies are asked to speak to one another at least once per week and each buddy pair brings in a snack for the group once.

Patients with any kind of infertility diagnosis may attend, including those with endometriosis, ovarian dysfunction, advanced age, male factor, premature ovarian failure, recurrent miscarriage, tubal blockage, and unexplained infertility. The groups include married heterosexual women, single women, lesbian women, and women with secondary infertility (although secondary patients may only have one child, women with more than one child are referred for individual counseling since their presence would be likely to upset the primary patients).

Table 19.1 outlines each session of the program, and every session follows a similar schedule, as can be seen in Table 19.2. Each session incorporates relaxation training, social support, and a new stress-management strategy. Despite the fact that the first half hour of social support is optional, virtually all participants choose to attend. This is the time to share their stories, compare experiences, and complain about their husbands/mothers-in-law/doctors.

Table 19.1 Sessions of the Mind/Body Program for Infertility

1. Group leader and peer counselor introductions, research on the stress/infertility connection, the physiology of the relaxation response, participant and partner introductions, program mechanics[a]
2. Physiology of diaphragmatic breathing, mini relaxation exercises, effective communication
3. The art of self-nurturance, how to reintroduce joy into one's life
4. The impact of lifestyle behaviors on fertility: weight, smoking, alcohol, exercise. The safety and efficacy of alternative medicine approaches
5. Introduction and experiential exercise of hatha yoga
6. Introduction to cognitive restructuring
7. All-day Sunday session—couples yoga, the use of humor to reduce stress, goal setting, couples' communication[a]
8. Completion of cognitive restructuring
9. The impact of emotional expression on health, journaling. Guest lectures from prior participants who went on to adopt or do donor egg[a]
10. Assertiveness, goal setting, summary, goodbyes

[a]Husbands/partners attend these sessions.

Table 19.2 Outline of Each Mind/Body Session

30 min	Optional sharing support time
15 min	Relaxation exercise (different one each week)
10 min	Patients pair up to discuss individual progress
30 min	Group discussion on how members are doing incorporating mind/body skills into their lives, review of previous week's assignment
10 min	Brief lecture by the group leader on the topic of the evening
30 min	Experiential exercise on evening's topic
20 min	Group discussion on topic, Q&A
5 min	Mini relaxation exercise

The program is designed to treat patients' anxiety first, so the first two sessions are dedicated to relaxation training. The next one is focused on self-nurturance, after which lifestyle habits are addressed. The current research on the impact of lifestyle behaviors is presented, such as the impact of smoking on IVF outcome, and participants are encouraged to discontinue smoking, limit their alcohol and caffeine intake, decrease the intensity of their exercise routine, maintain a healthy weight, and avoid alternative medicine methods such as herbs. The next sessions are dedicated to cognitive approaches to stress reduction, such as cognitive restructuring, journaling to express negative emotions, and effective communication strategies. One of the sessions includes guest lectures by prior participants who moved on to either adoption or egg donation.

Husbands/partners attend three of the ten sessions: the first introductory session, the Sunday session that is focused on couples' communication and pleasure, and the ninth session where the men meet as a group with a male therapist to discuss how they are handling the crisis of infertility.

At the first session, each participant is asked to describe what they hope to get out of the program, that is, where they hope to be by the tenth session. Thus, at the tenth session, each patient is asked whether or not they reached their goal. This tends to be a very emotional time, since each patient recounts her emotional state a mere 10 weeks ago and thanks the group, and group leader, for helping her get to a much healthier place.

At the tenth session, participants complete a similar but shorter questionnaire to the one they completed prior to the intake. Each patient is offered an appointment with the group leader to review their progress, compare their pre- with their postprogram status, and set goals for their continued improvement.

Patients consistently experience statistically significant reductions in all measured physical and psychological symptoms. But, perhaps more important, their attitude toward their infertility changes. As opposed to their sole identity as an infertile woman at the intake, they leave as healthy active women who happen to be experiencing infertility. They don't cry for days when they start to menstruate, they tolerate pregnancy announcements from others, and they feel more comfortable meeting their own needs, such as skipping baby showers or not visiting friends with newborns. Perhaps one of the most unexpected side effects of the program is the participant's willingness to try avenues that did not feel tolerable prior to participation, such as trying IVF or deciding to pursue donor egg, or adoption.

SUMMARY

Women experiencing infertility report significant levels of emotional distress. Their distress can make them difficult to treat, may make treatment less effective, and increases their tendency to drop out of treatment that might have been successful for them. Psychological interventions can decrease psychological symptoms and are associated with increases in pregnancy rates. A mind/body approach can satisfy the numerous needs of patients, including decreasing distress, increasing social support, increasing the chance of pregnancy, and helping them move on to alternative treatments, including assisted reproductive technology (ART) and third-party reproduction.

REFERENCES

1. Anderheim L, Holter H, Bergh C, et al. Does psychological stress affect the outcome of in vitro fertilization? Hum Reprod 2005; 20:2969–2975.
2. Domar AD, Broome A. The prevalence and predictability of depression in infertile women. Fertil Steril 1992; 58:1158–1163.
3. Domar AD, Zuttermeister PC, Friedman R. The psychological impact of infertility: a comparison to women with other medical conditions. J Psychsom Obstet Gynaecol 1993; 14:45–52.
4. Chen TH, Chang SP, Tsai CF, et al. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004; 19:2313–2318.
5. Domar AD. Infertility and the mind/body connection. The Female Patient 2005; 30:24–28.
6. Lintsen AME, Verhaak CM, Eijkemans MJC, et al. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Hum Reprod 2009; 24:1092–1098.
7. Klonoff-Cohen H, Chu E, Natarajan L, et al. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril 2001; 76:675–687.

8. Klonoff-Cohen H, Natarajan L. The Concerns During Assisted Reproduction Technologies (CART) scale and pregnancy outcomes. Fertil Steril 2004; 4:982–988.
9. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. Hum Reprod 2005; 20:1324–1332.
10. Land JA, Courtar DA, Evers JL. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. Fertil Steril 1997; 68:278–281.
11. Olivius K, Friden B, Lundin K, et al. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2002; 77:505–510.
12. Hammarberg K, Astbury J, Baker H. Women's experiences of IVF: a follow-up study. Hum Reprod 2001; 16:374–383.
13. Olivius C, Friden B, Borg G, et al. Why do couples discontinue in vitro fertilization treatment? A cohort study. Fertil Steril 2004; 81:258–261.
14. Domar AD, Smith K, Conboy L, et al. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertil Steril 2010; 94:1457–1459.
15. Shroder AK, Katalinic A, Diedrich K, et al. Cumulative pregnancy rates and drop out rates in a German IVF programme: 4102 cycles in 2130 patients. Repro Biomed Online 2004; 5:600–606.
16. Smeenk JM, Verhaak CM, Stolwijk AM, et al. Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. Fertil Steril 2004; 81:262–268.
17. Eisenberg ML, Smith JF, Millstein SG, et al. Predictors of not pursuing infertility treatment after an infertility diagnosis: examination of a prospective US cohort. Fertil Steril 2010; 94:2369–2371.
18. Herbert DL, Lucke JC, Dobson AJ. Depression: an emotional obstacle to seeking medical advice for infertility. Fertil Steril 2010; 94:1817–1821.
19. Terzioglu F. Investigation into effectiveness of counseling on assisted reproductive techniques in Turkey. J Psychosom Obstet Gynaecol. September 2001;22(3):133–141.
20. de Klerk, Hunfeld JA, Duivenvoorden MA, et al. Effectiveness of a psychological counseling intervention for first-time IVF couples: a randomized controlled trial. Hum Reprod 2005; 20: 1333–1338.
21. Domar AD, Clapp D, Slawsby EA, et al. Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 2000; 73:805–811.
22. Domar AD, Clapp D, Orav J, et al. The impact of group psychological interventions on distress in infertile women. Health Psychol 2000; 19:568–575.
23. Hosaka T, Matsubayashi H, Sugiyama Y, et al. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. Gen Hosp Psychiatr 2002; 24:353–356.
24. Domar AD, Backman K, Alper M, et al. The impact of a mind/body program on pregnancy rates in IVF patients. Presented at the annual meeting of ASRM, Atlanta, Georgia, October, 2009.
25. Boivin J. A review of psychosocial interventions in infertility. Soc Sci Med 2003; 57:2325–2341.
26. Hammerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rates. Hum Reprod 2009; 15:279–295.
27. Domar AD, Seibel MM, Benson H. The mind/body program for infertility: a new behavioral treatment approach for women with infertility. Fertil Steril 1990; 53:246–249.

20 Infertility counseling and the role of the infertility counselor

Jeanie Ungerleider, Terry Chen Rothchild, and Lynn Nichols

INFERTILITY AS A CRISIS

Infertility is a medical condition that can affect every part of an individual's or couple's life. It may challenge the ways in which people feel about themselves and their relationships with their partner, family, and friends. It often impacts their work environment and general outlook on life. Few situations in life are as challenging and overwhelming. Because of this, infertility is considered a life crisis.

For those going through infertility, this often is the first time that an experience in life may feel totally beyond their control. Most people assume that if they only work hard enough, they will succeed and achieve their goals, including when to become parents. Being faced with infertility often runs counter to the experiences and expectations of individuals and couples about life. Not being able to get pregnant when they want to and feeling a lack of control in this area can be frustrating and frightening. These feelings can then get amplified by the disappointment of repeated failed treatment. Indeed, the uncertainty as to whether they will ever conceive and have a healthy baby can create mounting anxiety. The infertile couple is surrounded by peers who are pregnant with their first, second, or third child, while they struggle with infertility treatments and feeling increasingly resentful, angry, and isolated from their usual supports.

Infertility is a crisis of identity that can challenge one's sense of self and self-worth. It can impair one's definition of who they are and whether they will ever have a meaningful place in the world. For women, infertility challenges their long-held assumptions of being mothers someday. The more that a woman's self-identity is defined by being a mother, the more at risk she is for psychological distress and feelings of inadequacy. The longer that infertility continues, the more a sense of helplessness and hopelessness can take over, which can lead to greater depression. A diagnosis of male factor problem can feel devastating for the man. This finding can challenge his sense of masculinity, potency, and identity.

Factors contributing to different people's coping styles include personality differences, family history, and life experiences. These factors can shape how people experience and handle this particular life crisis. Moreover, women and men can demonstrate very different ways of coping with the diagnosis of infertility. Women often feel anxious and depressed because they are mindful of the limits of their biological clock. There is the heightened awareness of the urgency of time and a painful reminder of disappointment each month when there is no pregnancy. Women are sometimes angry with themselves or their partners for not starting to build their family sooner. They are burdened with feelings of guilt and regret about their delay. In some cases, for women who had a prior termination of pregnancy, they may come to feel that their infertility is a punishment for having had an earlier abortion.

Women, who are faced with infertility, often want to discuss their feelings and concerns with their partners, which can dominate their conversations when the couple spends time together. Generally speaking, men may tend to respond with optimism, assuring their partner of a positive outcome. Not wanting to fuel or add to their partner's distress, they may wish to limit or avoid conversation about infertility. The couple's growing sense of feeling disconnected from each other can add to an already existing sense of isolation and alienation from the outside world. Tensions such as these often interfere with the couple's sexual relationship. No longer is their lovemaking pleasurable and intimate. Sex becomes a task to accomplish the goal of conception. When the woman and man's styles are in such contrast, it can interfere with their going forward with infertility treatment as a couple.

A couple was referred to the infertility counselor by their physician because they expressed conflict over how aggressive they wanted their infertility treatment to be and showed difficulty with decision-making. The husband, age 36, was annoyed by his wife's insistence on seeking infertility treatment just six months into their marriage. His wife, age 39, was convinced that she would have problems conceiving because of her history of erratic menstrual cycles. The husband complained that his wife had become totally obsessed and preoccupied with having a baby to the exclusion of his needs. The counselor met weekly with the couple, helping them to communicate more effectively with each other. Their increased ability to partner together and to appreciate each of their different coping styles allowed this couple to proceed more effectively with infertility treatment.

THE ROLE OF THE COUNSELOR IN AN INFERTILITY PRACTICE

Most major infertility practices have licensed independent clinical social workers (LICSWs) or psychologists available who specialize in infertility counseling. Many of these clinicians are members of the American Society for Reproductive Medicine (ASRM) and the Mental Health Professional Group of ASRM that offer practice guidelines and guidance for the mental health professionals. The role of the infertility counselor is multifaceted and ever-changing depending on the request of the physician, the expressed needs of the individual or couple, and the level of distress and crisis in their life. The counselor can serve the role of a clinical evaluator, consulting member of the health care team, supportive counselor, bereavement counselor, patient advocate, or more broadly, psychotherapist. Furthermore, the infertility counselor can make referrals to resources in the community and be a liaison to other mental health professionals, such as psychopharmacologists and psychotherapists, on behalf of the health care team. The roles of the infertility counselor can shift with the individual or couple over time and reflect the complex process of infertility treatment as well as people's responses to their treatment and changing needs.

Counseling can offer support in dealing with the unique stresses of ongoing medical treatments and the uncertainty of outcome, including the possibility of unsuccessful treatment cycles. If an individual or couple is having a difficult time going through the medical process, seeing a counselor one-on-one can help address the issues that are specific to the individual or couple and provide the needed support and strategies.

Counseling is helpful for those who are having difficulty making informed treatment decisions or choosing treatment options. It is also useful for those who have experienced a miscarriage and are grieving this very powerful and real loss. The counselor can offer acute bereavement counseling in response to the immediate loss as well as assist them in the resolution of their grief overtime. The counselor can also provide resources to bereavement support groups, readings, and Web sites. Being able to do some grief work initially will help those who have faced loss to move forward with the medical process with more emotional resiliency.

Counseling is also recommended for people who are facing the end of medical treatment and are having difficulty making this decision, or wishing to discuss other options and alternatives, such as the use of donor egg or donor sperm, gestational care arrangement, adoption, or childfree living. Some of these issues are covered later in this chapter.

If the individual or couple is experiencing stress, depression, or anxiety to a degree that is significantly affecting their life or making it hard to enjoy life, it is advisable to refer them to a counselor before any medical treatment begins. As outlined in the ASRM Fact Sheet on Infertility Counseling and Support, signs and symptoms to consider include the following:

- Persistent feelings of sadness, guilt, or worthlessness
- Loss of interest in usual activities and relationships
- Agitation and anxiety
- Constant preoccupation with infertility
- Difficulty concentrating and remembering
- Change in appetite, weight, or sleep patterns
- Social isolation
- Increased use of alcohol or drugs

- Increased mood swings
- Marital conflicts
- Other current or past stress that heightens infertility distress

In making a clinical assessment of the individual's or couple's needs, the counselor can determine the most appropriate treatment modality. This can be in the form of individual counseling, couples counseling, a support group, a mind/body program, or a combination of these options. In individual and couples counseling, the counselor can help sort out feelings of how their infertility has impacted them and their partner as well as help them deal with family, friends, and the fertile society. Couples learn ways to strengthen their relationship and develop skills to navigate the emotional roller coaster of infertility. A peer support group can help reduce the feelings of isolation and provide a support network, and additionally, a mind/body program can teach self-care skills and address lifestyle changes that can have beneficial effects for a lifetime. It is generally agreed that the outcome for those people who seek professional help in some form is much better than for those who choose to remain socially isolated and grieve alone, especially if infertility treatment is prolonged and disappointing.

The following case demonstrates the various roles that an infertility counselor can provide over time in helping a person with his/her emotional needs and assisting as part of the health care team:

> A 37-year-old married woman presented with depression and crying whenever she got her period. She was obsessed about getting pregnant for the last 1½ years. While quite motivated, she stated that she was very anxious about the medical process and reported a history of panic reactions based on childhood fears. There were "worriers" in her family, and her own anxiety had worsened as each treatment cycle was met with failure. The counselor offered her opportunities to safely talk about and examine her fears, helped her gain perspective on overwhelming feelings and issues, helped her identify what resources and assistance she needed most at each stage of her cycle, and shared relevant information with her physician and nurse coordinator so that she felt well cared for by her whole team. Based on ongoing discussions and increasing trust with the counselor, this woman was able to see how unable she was at advocating for herself in the initial stages of medical treatment given her overwhelming level of distress, which was in sharp contrast to her effectiveness as a manager at her job. During counseling sessions, she also gained insight into how not allowing her husband to participate in her treatment served to protect her husband, but consequently, provided inadequate care to herself. She recognized this as a pattern that was counterproductive to them both. After undergoing four in vitro fertilization (IVF) cycles with the needed emotional support from her whole health care team and husband, she went on to have a successful pregnancy and delivery.

A woman can bring a complicated history, such as a trauma history or other past stress, which can heighten infertility distress. With the counselor's understanding of the cause of her distress, the counselor can effectively help to facilitate the woman's care with her health care team and intervene when necessary in a particular area of concern in order to assist her in going forward with treatment.

> A woman presented with anxiety and stress as her first IVF procedure approached and questioned whether she could go forward. She was increasingly having difficulty sleeping and concentrating at work. In the assessment with the counselor, she revealed a history of emotional and sexual abuse. She realized that she was terrified of having the procedure done by a physician whom she would not know and was not scheduled to meet until the day of the procedure. She was also fearful of having anesthesia, which she had never experienced. The counselor was able to advocate on behalf of the woman and arranged for her to meet briefly with the physician, OR nurse, and anesthesiologist prior to the day of her IVF procedure. This helped diminish her anxiety considerably and made her feel well cared for. The staff also benefited from the advance meeting and understanding of this special situation.

THE ROLE OF THE INFERTILITY COUNSELOR IN ASSISTED CONCEPTION

Newer ways of having a family with the use of donor egg, donor sperm, gestational carrier arrangement, preimplantation genetic diagnosis (PGD) for gender selection, and embryo donation have become increasingly successful for individuals and couples to have a child.

These choices of family building raise unique social, emotional, and ethical issues. As part of most IVF programs, it is considered invaluable for people to meet with an infertility counselor to discuss these complex issues.

Donor Egg or Donor Sperm Consultation

When the use of a third party in the reproductive process (donor egg or donor sperm) is recommended to infertile individuals and couples, new sets of concerns and feelings arise. These include feelings about the medical condition that necessitated the use of a donor. Additionally, the loss of the genetic tie to the prospective mother or father and its meaning may become central. Practical issues such as disclosure must also be addressed. While the decision to tell the child about its genetic origins is a personal one, it is an issue that should be explored with the couple before treatment begins. Those coming into infertility clinics with the hopes of creating their own child have often gone through and continue to go through a multitude of emotional experiences from positive anticipation to frustration, disappointment, and continued loss. Here the counselor can continue to assist couples manage the emotional roller coaster associated with infertility treatment.

The topics covered in the psychoeducational consultation of third-party reproduction may include transitioning from a traditional form of treatment to the use of a third party; the feelings involved in making this decision; choosing an anonymous or known donor and the benefits and challenges associated with either choice; issues of disclosure, including when and how to tell the child, the notion of privacy versus secrecy, and how to discuss disclosure with family and friends; transitioning to parenthood and parenting at an older age, if applicable; and the possibility of treatment failure and alternatives for future planning.

In her role as clinical evaluator and consulting member of the health care team, the counselor also participates in the screening of the anonymous and known egg donor. While the donor undergoes a thorough medical screening, it is the responsibility of the counselor to conduct a psychosocial evaluation. The purpose of this portion of the donor screening is to have an understanding of the donor's current life situation as well as assess her personal and family psychiatric history. It is also to determine whether or not she is aware of and prepared to meet the responsibilities and demands present in an egg donation cycle. The counselor follows the ASRM general guidelines for the psychological assessment of oocyte donors and recipients to help determine if a donor is an appropriate candidate. It is also the responsibility of the counselor to inform the donor about the potential emotional benefits and risks associated with egg donation and help her determine if the decision to serve as a donor is well thought out and in her best interest, thus helping her make a psychologically informed consent.

In instances where a known donor is considered, it is important for the infertility counselor to explore and discuss with the recipients and donor together their feelings about the relationship and future expectations between all parties, including the future child. It is essential that everyone involved meet at the time of the medical screening and be in agreement with decisions that have the potential to affect a future family.

Gestational Carrier Arrangement Consultation

The use of gestational carrier arrangement is rarely the first choice for family building in assisted conception. More often, people come to this after exhausting other options, such as intrauterine insemination (IUI) and IVF. Medical conditions on the part of the woman, such as the loss of or impaired uterus, can also determine the use of gestational carrier arrangement in some cases. The most common gestational carrier arrangement these days is for the intended or prospective mother or an egg donor to provide the egg and the intended or prospective father or sperm donor to provide the sperm. The resulting embryo is transferred to the gestational carrier, who has no genetic connection to the child.

> After multiple attempts with assisted conception, including several IVF cycles and two recent miscarriages, a couple was recommended gestational carrier arrangement as another option. The woman showed diminished egg quality and quantity, so egg donation was also recommended to increase the couple's chance of success. Counseling was provided to them at this point to help them accept having another woman carry their child and understand the

various psychological issues related to both gestational carrier arrangement and egg donation. The couple went on to secure a gestational carrier and after two attempts, their gestational carrier got pregnant and delivered a term child for this couple, who had gone through many years of trying on their own.

The role of the professional counselor in gestational carrier arrangement consultation is to determine what is best for all the participants involved, including the existing children, and to foresee the range of psychological issues that occur in third-party reproduction and pregnancy and address these to the individualized, psychosocial situations of the participants. The standard practice is for the counselor to have the first consultation with the intended parents to discuss the psychological issues related to gestational carrier arrangement and to assist them in assessing their readiness to take part in a gestational carrier arrangement. This consultation is followed by one evaluative consultation with the prospective gestational carrier and her husband or partner to assess their psychological readiness to participate in a gestational carrier arrangement. Lastly, a joint consultation is provided to the intended parents and gestational carrier and husband or partner together to discuss and assess their readiness to take part in a gestational carrier arrangement with one another. This joint meeting is an important opportunity to define everyone's mutual expectations with regard to the nature of their relationship during the medical process, pregnancy, and after the delivery, as well as to discuss their agreement on potential decision-making ahead, such as twin pregnancy, selective reduction, or circumstances for the termination of a pregnancy.

The counselor also either provides or makes arrangement for standardized psychological testing of the prospective carrier as part of the screening process. This typically includes a personality test, such as the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) or the Personality Assessment Inventory (PAI), as well as another psychological assessment instrument, such as the Rorschach Comprehensive System, or measurements assessing the gestational carrier's capacity to cope with stress and the quality of her interpersonal relationships.

The evaluation of the carrier by the counselor is an in-depth process and also involves evaluation of her husband or partner as well. Many factors go into the selection of an appropriate gestational carrier, including understanding her motivation or underlying reason to be a gestational carrier for someone. It is important that she has had positive experiences with previous pregnancies and be raising a child of her own. It is critical to assess her psychosocial history and current life situation as well as her psychological history and emotional well-being. It is also important for the gestational carrier to have an adequate support system, in particular her husband or partner, who supports her wish to be a gestational carrier and helps her and her children during a pregnancy, especially should she require bed rest or hospitalized bed rest. She must be at peace about the relinquishment of the child to the intended parents. The goal is for the prospective gestational carrier to leave the program whole and unharmed and feel satisfied with the process and her relationship with the intended parents.

It is important for all participants involved to have legal, medical, and psychological consultations. Once the medical process is underway, ongoing psychological counseling for the intended parents on an as-needed basis as well as follow-up with their gestational carrier can be an option offered in an effort to help facilitate the gestational carrier process and support their relationship during the pregnancy and afterward. If participants are well matched and invested in the psychological preparedness and considerations, the experience can be mutually fulfilling and satisfying. Additionally, it is a wonderful opportunity to create a positive legacy for the forthcoming child.

In contrast to this group of infertile couples, there are also single adults, gay, and lesbian couples who enter infertility practices and look to the donor process or gestational care arrangement as a way of becoming parents. These groups of people, who have not experienced problems with infertility by and large, may not necessarily go through the same emotional experiences as the infertility group. The issue of loss, mourning, and grief may be quite different depending on their reason for treatment. Nonetheless, the use of a third party in the reproductive process does raise certain unique social, emotional, and ethical issues for all recipients, donors, and children. Additionally, with both of these groups, the infertility counselor has an opportunity to address concerns about how to raise these children as healthy

and wholesome beings and help children deal with information about their assisted conception in their various life stages.

Preimplantation Genetic Diagnosis for Gender Selection Consultation

Preimplantation genetic diagnosis or PGD is a technology used in conjunction with IVF to test for healthy embryos prior to transfer to the woman's uterus. One indication for performing PGD is when the couple is at risk for having a child with an inherited genetic disorder (i.e., cystic fibrosis, Tay–Sachs disease). A single cell is removed from each embryo and can be tested for the specific genetic disorders. Only embryos free of genetic abnormalities are selected for implantation. Prior to the advent of PGD, testing for genetic disorders was limited and could only be done during the first trimester of pregnancy. The woman would have to endure the stress of waiting for the results. If carrying a genetically abnormal fetus, she would be faced with the psychological trauma associated with decision-making around pregnancy termination. PGD now offers individuals the opportunity to determine healthy embryos prior to transfer, which also reduces much emotional distress with pregnancy.

PGD can also be performed to determine the chromosomal makeup of the embryo including an assessment of the sex chromosomes. There are now some IVF centers that offer PGD to determine the gender of the embryo. Gender selection can be used to eliminate those embryos of a certain gender with a transmittable genetic disorder. Some prospective parent(s) may have a strong gender preference and may request use of PGD for gender selection. Still others may choose PGD for family balancing. for example, if the couple already has a child or children of one gender and expresses the desire to have another child of the opposite gender. In this situation, all the embryos would be tested to determine their gender, and then the healthy embryos of the preferred sex would be transferred to the woman's uterus.

Sex selection raises various psychosocial, ethical, and controversial issues, such as if a couple has not yet had a child, should they be allowed to select the sex of their offspring? Just because the technology exists, should it be used in this way? Some IVF centers only offer sex selection for family balancing.

It is important for counseling to be available to individuals and couples who are considering PGD for gender selection to allow them to think through the unique psychosocial and ethical questions that are inherent in this technology. For example, if a person wants to have a female child, and they undergo IVF with PGD, and there are no healthy female embryos, would they transfer the healthy male embryos instead? If they decide not to transfer the healthy male embryos, then what would be the disposition plan for these newly created embryos? The possible options would be to consider freezing the embryos and postpone making any decisions, donating them for medical research, or donating the embryos to another couple or individual. They could also choose to discard the embryos. Thorough discussion of each of these choices needs to be carefully explored before commencing the IVF cycle. If there is a difference of opinion between the couple, they will need assistance in reaching a decision that they can both agree upon.

Embryo Donation Consultation

When a couple or individual has created embryos through infertility treatment with IVF and successfully completed their family building, they need to consider the disposition of the extra embryos that they no longer need. They could decide to continue to keep them frozen, paying a yearly storage charge until they are ready to make a final decision on disposition. With the success of IVF, there are now more than 400,000 extra frozen embryos stored in laboratories across the United States. The majority of recipients choose to dispose of their extra embryos or donate them for medical research. Still a few recipients will consider the option of donating their excess frozen embryos to others who are infertile and in need of embryos to build a family. Donated embryos can offer these people another viable way for family building. This can also be a practical way for single women or same sex couples to create their families. In addition to some IVF centers, there are also a few agencies, such as The National Embryo Donation Center, that help facilitate the donation of embryos.

There are several reasons for considering embryo donation. Recipients may not have been able to create healthy embryos with their own gametes, or be faced with a male or female

factor problem, or wish to avoid transmitting a genetic disease to their offspring. In some instances, recipients may favor embryo donation instead of one partner having a genetic link to the child and not the other. This would be a way for each parent to have an equal connection to their child. For some recipients, the cost is another major factor in their decision to use donated embryos. It is considerably less than paying for an IVF cycle with donor gametes. Becoming a recipient of embryo donation takes considerably less time than going through an adoption process. Finally, it gives the prospective mother the opportunity to experience pregnancy and bond with her baby from the beginning.

There are many more recipients who want donated embryos than there are people willing to donate. Often when an infertile couple finally achieves a successful pregnancy and then has a baby, they may initially consider donating their extra embryos to another couple or individual struggling to conceive. However, once they have their own child or children and become parents, the reality of donating their unused embryos takes on a very different meaning. Parents begin to think about the fact that their frozen embryos would become full genetic siblings to their children if they were to donate them to another person. Anticipating this possible reality raises a host of emotions, questions, and thoughts to consider.

Counseling for embryo donors and recipients is extremely helpful in thinking through the psychosocial, ethical, and legal issues unique to embryo donation. The Practice Committee of the ASRM and the Practice Committee of the Society for Assisted Reproductive Technology (SART) provide explicit 2008 Guidelines for Gamete and Embryo Donation. The complex and often charged emotions that embryo donation raises need to be thoroughly explored and understood. It is useful for both embryo donors and recipients to completely understand the implications of their decision in order to make a psychological informed consent. Before recipients can move forward with considering embryo donation, they need time to work through their loss of ever having a biological and genetic child with their partner.

Some of the issues to consider are as follows: Will they choose a known donor/known recipient situation? What kind of relationship would the donor family have with the recipient family? What would be the expectations of the relationship with the child who was created through embryo donation? Would the recipient's children and donor's children know about each other? And if so, when and how do they explain this unique situation to their children? In an anonymous embryo donation, the donors and recipients independently decide how much information to share about each other's family and if they would want the option to have contact with the child at 18 years or older.

Parents choosing to donate their extra embryos to an infertile couple or individual often feel tremendous empathy and identification with those who are struggling to conceive. Donating can be an opportunity to help another family in a very powerful way and at the same time be compatible with the donating couple's values and religious beliefs. For the donating couple, it can be a welcome solution if disposing of extra embryos or donating their embryos to medical research feels ethically and morally unacceptable to them.

SUMMARY

While the infertility counselor cannot predict or guarantee the outcome of the woman's infertility treatments, the counselor can help make the process as supportive and helpful as possible. The individual or couple generally value the team approach and express appreciation for their health care providers' attention to their medical, physical, emotional, and psychosocial well-being.

In the near future, assisted reproductive technologies will become even more sophisticated, with the availability of ovum freezing and more extensive use of preimplantation genetic testing. These new advances will open up more complex ethical, emotional, and psychosocial issues. With the increased success of the assisted reproductive technologies, there are new ways to create families. It is possible to have numerous people involved in the creation of a child. They can include the ovum donor, the sperm donor, the gestational carrier, and the intended parents who will be raising the child. Such complex options for family building necessitate careful understanding of the issues involved and exploration of their implications for the individual, couple, and future child. The infertility counselor's role is ever expanding as people make use of these new pathways to parenthood.

Box 1 Where to find an infertility counselor?

Mental health professionals, including social workers, psychologists, and psychiatrists, are trained to evaluate and treat individuals and couples who are in crisis. Because of the complexities of infertility and the treatment options that are available, individuals and couples would benefit most from a referral to a mental health professional with expertise in the field of infertility. Besides getting a referral from their own physician who specializes in infertility treatment, people can turn to RESOLVE, the American Fertility Association (AFA), and the American Society for Reproductive Medicine (ASRM) as valuable resources for seeking out qualified mental health professionals in their community as well as information.

RESOLVE: The National Infertility Association
1760 Old Meadow Road
McLean, VA 22102
703-556-7172
http://www.resolve.org

American Fertility Association (AFA)
315 Madison Ave
New York, NY 10017
888-917-3777
http://www.theafa.org

The American Society for Reproductive Medicine (ASRM)
1209 Montgomery Highway
Birmingham, AL 35216
205-978-5000
http://www.asrm.org

How to learn more about adoption?

The first step is to talk with a mental health professional about the emotional and practical issues related to adoption. There are various types of adoption, including open/identified or closed adoption as well as domestic and international. The following resources are provided for additional information:

National Council for Adoption
225 N. Washington Street
Alexandria, VA 22314-2561
703-299-6633
http://www.adoptioncouncil.org

Adoption Community of New England
45 Lyman Street
Westborough, MA
508-366-6812
http://www.adoptioncommunityofne.org

RESOLVE: The National Infertility Association
1760 Old Meadow Road
McLean, VA 22102
703-556-7172
http://www.resolve.org

21 Insurance and coding issues

Steven R Bayer and Karen Parlee

Before any medical services are provided, it is essential that the patient's insurance coverage be investigated. This is a dual responsibility of both the patient and the medical practice. This will help to insure that any services that are rendered will be properly reimbursed and will eliminate the chance that the patient will receive any unexpected bills. Some of the important insurance issues regarding infertility services are discussed below. In addition, guidelines for current procedural terminology (CPT) coding for infertility services are presented.

WHEN SHOULD THERE BE AN INVESTIGATION OF THE INSURANCE COVERAGE?

When the first appointment is made, we encourage all our patients to educate themselves on the limits of their insurance coverage for infertility services. At the initial consultation, documentation of medical insurance coverage for both partners should be reviewed and verified. An updated insurance card should be copied and placed in the patient's chart. Verification of infertility benefits should be obtained by contacting the insurance company or reviewing the insurance policy. The extent and the limitations of coverage should also be determined. If there are any restrictions in the insurance coverage, it is important that this is discussed with the couple before they undergo any medical services. This information needs to be conveyed to the medical team as well so that treatment can be tailored according to their coverage. For instance, if there is a cap on coverage it may be worthwhile to try a few cycles of clomiphene citrate/intrauterine insemination (CC-IUI) treatment but bypass the more costly follicle stimulating hormone/intrauterine insemination (FSH-IUI) treatment and go directly to IVF. Any conversations that our financial coordinators have with insurance companies and patients regarding coverage are documented in the medical record so that they can be referred to in the future. At our center, we have the patients sign a waiver that they are responsible to know their benefits and are financially responsible for any uncovered services (Fig. 21.1).

If the insurance company denies coverage for infertility services, the couple may have recourse. The first option is that the couple can present their case in front of the appeals board of the insurance company. In some cases, legal representation will maximize the results of the appeals process. The other option is that the couple can contact the state insurance commissioner, who acts on behalf of consumers. Finally, couples who do not have any insurance benefits should be encouraged to look for other insurance plans that may provide coverage for infertility services.

It is also important to keep tabs on the patient's insurance plan. Many patients change jobs or their employers change the insurance plans that they offer. At every visit, it is our policy to ask patients if their current insurance plan is still in effect.

WHAT STATES HAVE MANDATED INFERTILITY BENEFITS?

Infertility treatment has been viewed as elective and many insurance companies have chosen not to pay for it. In 1987, Massachusetts passed a bill that defined infertility as a medical diagnosis and therefore mandated insurance companies in the state to pay for infertility treatment. Other states have insurance mandates in place that are presented in Table 21.1. If you reside in a state that does not have mandated insurance benefits for infertility, you can contact RESOLVE (http://www.resolve.org), a patient advocacy organization to find out if there is any pending legislation. Even if your state does have mandated benefits, restrictions can still exist regarding the extent and types of infertility treatment that are covered. In addition, within mandated states, privately insured companies often can limit or eliminate infertility services as a covered benefit.

Understanding Your Insurance Benefits

We know that insurance and financial matters can be complicated. This document is designed to outline important insurance and financial information that you need to know while receiving services at our center.

- Please contact your insurance company as it is your responsibility to obtain your infertility benefits. Your insurance company customer service representative will help you to understand your plan**, what it covers and what it does not.**
- Your insurance company may require referrals from your primary care physician for your visits. It is your responsibility to obtain these referrals. If you are not able to obtain a referral from your primary care physician you will be charged for that visit.
- If your insurance plan imposes a dollar limit on your treatment, you are responsible for keeping track of the money paid by your insurance. Once you have met this dollar maximum, you will be responsible for the cost of services that are provided to you.
- Please notify us **immediately** of any changes to your insurance. If your coverage terminates while you are undergoing treatment, you will be financially responsible for charges incurred during your lapse in coverage. Due to the pre-authorization requirements of the insurance companies, if you change insurance plans while undergoing a treatment cycle, your cycle may be delayed or cancelled and you may be responsible for the cost of that treatment cycle. If you proceed with any treatment that has not been approved by your insurance company, you will be responsible for those charges.
- Many patients choose to freeze sperm and/or embryos at our facility. This may or may not be a covered benefit under your plan. Please check with your insurance company to determine if these services are a covered benefit for you.
- There are annual storage charges for frozen embryos as well as frozen sperm that are not covered by insurance. Your financial counselor can provide you with our current prices for these services if they apply to you.
- We require 24 hours' notice if you are canceling your appointment. If you do not cancel your appointment with 24 hours' notice or if you do not appear for your appointment you may be responsible for a cancellation fee of up to the full cost of the visit.

MY SIGNATURE BELOW INDICATES THAT I HAVE READ AND UNDERSTAND THE INFORMATION PROVIDED IN THIS DOCUMENT.

Please bring this document with you to your appointment and give to your financial counselor.

_____ _____

(Print Name) (Date)

_____

(Signature)

Figure 21.1 Insurance waiver form.

Table 21.1 State Infertility Coverage

State		Mandate to		IVF coverage		IVF Tx
	Enacted	Cover	Offer	Included	Excluded	Only
Arkansas	1987	X[a]				X
California	1989		X		X[b]	
Connecticut	1989	X		X		
Hawaii	1987	X				X[c]
Illinois	1991	X		X[d]		
Louisiana	2001				X	
Maryland	1985	X[e]				X
Massachusetts	1987	X		X		
Montana	1987	X[f]				
New Jersey	2001	X		X		
New York	1990				X[g]	
Ohio	1991	X[f]				
Rhode Island	1989	X		X		
Texas	1987		X			X
West Virginia	1977	X[f]				

[a]Lifetime maximum benefit of not less than $15,000. [b]Excludes IVF but covers GIFT. [c]A one-time benefit covering all outpatient IVF expenses. [d]Limits first-time attempts to four oocyte retrievals. If a child is born, two complete oocyte retrievals are covered. Businesses with 25 or fewer employees are exempt. [e]Businesses with 50 or fewer employees are exempt. [f]Applies to health maintenance organizations (HMOs) only. [g]Provides coverage for the "diagnosis and treatment of correctable medical conditions." Does not consider IVF a corrective treatment.
Source: Data obtained from the American Society for Reproductive Medicine. Available at: http://www.asrm.org.

CODING AND BILLING ISSUES

After medical services have been provided, the next step is to get reimbursed from the insurance company in an expeditious fashion. This is achieved by submitting a claim to the insurance company describing the procedures that were performed along with supporting diagnosis codes. The reference for diagnostic coding is *The International Classifications of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The manual has been revised and the changes in the 10th revision (*ICD-10-CM*) will be implemented in 2013. Complete Procedure Terminology (CPT) coding is based on a numerical system that identifies the procedure that was performed. Accurate CPT coding helps to maximize reimbursements and to avoid costly audits by insurance companies. A complete review of CPT coding is beyond the scope of this handbook. CPT coding is a complicated process that is constantly changing. All physicians need to have an understanding of in the intricacies of the coding process. The American Medical Association (AMA) publishes an annual update on CPT coding. In addition, the American College of Obstetrics and Gynecology (ACOG) publishes an annual update of changes in the specialty. The coding for specific procedures regarding infertility treatments is discussed below.

Evaluation and Management CPT Codes

The evaluation and management (E/M) CPT codes are applied to services provided in the office. The E/M services include *new* patient office visits (CPT codes 99241–99245, 99201–99205) and repeat visits (CPT codes 99211–99215). A new patient is one who has not been seen in consultation by the treating physician or by another physician in his/her group in the past three years. There are two choices for coding after a new patient office visit:

1. If a physician or other appropriate authority has requested an opinion regarding the evaluation and treatment of a particular medical problem, then the consultation CPT codes are used (99241–99245). Some insurers no longer reimburse for 99211–99245. In that case, you would need to use 99201–99205. After the consultation, a letter needs to be sent to the referring physician. These consultation codes can only be used once.

After a physician has assumed care of the patient, for any follow-up consultations, the repeat visit codes should be used (99211–99215).
2. If a new patient has not been referred by another physician, the CPT codes 99201–99205 should be used.

The key components of the E/M codes include the history, physical examination, medical decision-making, counseling, coordination of care, nature of presenting problem, and time. The first three components of this list (history, physical examination, and medical decision-making) are the key components that determine the level of coding.

1. For the new patient visits (99241–99245, 99201–99205), all three key components need to be performed and documented.
2. For repeat visits (99211–99215), two out of the three key components should be performed and documented.

However, in many cases, at the time of the office visit the majority of the physician's time is spent counseling the couple and the key components necessary for the coding are not performed. In these situations, the time spent can be the controlling factor to determine the level of the coding but it needs to be documented in the chart. An excerpt from the AMA CPT coding manual addresses this issue:

> In the case when counseling and/or coordination of care dominates (more than 50%) the physician/patient encounter (face-to-face time in the office or other outpatient setting or floor/unit time in the hospital), then time may be considered the key or controlling factor to qualify for a particular level of E/M services. The extent of counseling and/or coordination of care must be documented in the medical record.

Therefore, we document in our medical records the following statement:

> "A total of ____minutes was spent face to face with the patient and >50% of the time was spent in counseling."

The amount of face-to-face time (in minutes) needed to determine the level of coding is described in the AMA CPT handbook and is as follows:

99241 15′	99201 10′	99211 5′
99242 30′	99202 20′	99212 10′
99243 40′	99203 30′	99213 15′
99244 60′	99204 45′	99214 25′
99245 80′	99205 60′	99215 40′

To aid our physicians with correct CPT coding, we have listed the encounter times next to the correct CPT code on the fee ticket that is filled out after the office visit (Fig. 21.2).

Coding for Specific Office Procedures

The CPT codes that can be used for various office procedures are listed below. If a consultation takes place either before or after the procedure is performed, then the appropriate E/M code should be selected but a modifier (–25) must be added. Time spent discussing the procedure or reviewing the consent with the patient is felt to be inclusive in the code of the procedure and should not be billed separately.

A. Endometrial biopsy[a]
   81025—urine pregnancy testing
   58100—performance of endometrial biopsy

[a]In some cases, a paracervical block (CPT code—64435) and/or a cervical dilation (CPT code—57800) are necessary to complete these procedures. If so, these procedure codes should be submitted for reimbursement.

Name:	DOB	Clinician	Site:
Service Date:	Primary Insurance:		Referral #
Reason:	Initials:	Is there a co-pay? Y / N	Amount-
Outstanding balance:	Global: Y / N	How was it paid?	
	Initials:	Any change in address/insurance? Y / N	Initials

OFFICE VISITS			DIAGNOSIS		DIAGNOSIS	
New (referred)	**PE or Time**		**INFERTILITY**		**GYNECOLOGY**	
LEVEL 1	(15)	99241	Anovulation	628.0	Pain	
LEVEL 2	(30)	99242	Cervical	628.4	Abdominal	789.67
LEVEL 3	(40)	99243	Male factor	628.8	Dysmenorrhea	625.3
* LEVEL 4	(60)	99244	Tubal factor	628.2	Dyspareunia	625.0
LEVEL 5	(80)	99245	Uterine factor	628.3	Pelvic	625.9
New (not referred)	**PE or Time**		Unexplained	628.9	PCO	256.4
LEVEL 2	(20)	99202	Other, specified origin	628.8	Premenstrual symptom	625.4
LEVEL 3	(30)	99203			Polyp Ð endometrial	621.0
LEVEL 4	(45)	99204	**ENDOCRINE**		Ð cervical	622.7
* LEVEL 5	(60)	99205	Amenorrhea	626.0	Vaginitis	616.10
Repeat office visit	**Time**		Hirsutism	704.1	**PREGNANCY**	
LEVEL 1	(5)	99211	Hyperprolactinemia	253.1	Supervision	V23.0
LEVEL 2	(10)	99212	Other ovarian dysfunction	256.8	Twin pregnancy	651.00
LEVEL 3	(15)	99213	PCO	256.4	Triplet pregnancy	651.10
* LEVEL 4	(25)	99214	Premature ovarian failure	256.31	Miscarriage: SAB	634.90
LEVEL 5	(40)	99215	**GYNECOLOGY**		Threatened	640.03
Prenatal visit	(15)	99213	Adenomyosis	617.0	Missed	632
	(25)	99214	Adhesions Ð tubal/pelvic	614.6	Habitual AB	629.9
			Annual gyn exam	V72.31	Ectopic pregnancy (tubal	633.10
Post-op visit		99024	Asherman syndrome	21.5	Ectopic pregnancy (presumed)	633.90
Annual GYN Exam			Bleeding		**OTHER DIAGNOSES**	
18-39YRS	NEW PATIENT	99385	Menorrhagia	626.2	Egg donor	V99.9
	ESTABLISHED	99395	Abnormal uterine bleeding	626.6	Genetic counseling	V26.3
40-64YRS	NEW PATIENT	99386	Unspecified	626.9	Gestational carrier	V99.9
	ESTABLISHED	99396	Cervical polyp	622.7	TDI Ð single Ð female	V26.8
			Cervical stenosis	622.4	Other specified procreative mgt	V26.8
CANCELLATION		CAN	Cervical dysplasia	622.10	Previous tubal ligation	V26.51
NO SHOW		NO SHOW	Chronic anovulation	626.1	Previous vasectomy	V26.52
			Dysmenorrhea	625.3	**Ultrasound procedures**	**Diagnosis**
Hospital Care Services			Dyspareunia	625.0	Follicle Ð initial complete 76830	628.9
Initial inpatient visit	(50)	99222	Dysuria	788.1	Follicle-F/U 76857	628.9
Repeat inpatient visit	(25)	99232	Endometrial hyperplasia	621.30	Prenatal (initial) 76817	V23.0
Discharge day	(30)	99238	Endometrial polyp	621.0	Prenatal (follow-up)	
Emergency room visit			Endometriosis:		Bleeding 76815	640.03
Level 3 (Pt discharged)		99283	of ovary	617.1	? Miscarriage 76815	632
Level 4 (Pt admitted)		99284	of fallopian tube	617.2	Twin 76815	651.00
			of pelvic peritoneum	617.3	Triplet 76815	651.10
OFFICE PROCEDURES			Herpes genitalia	054.10	Age > 34 years 76817	659.53
Cervical dilation		57800	Leiomyoma	218.9	R/O ectopic 76817	633.90
Cervical polyp removal		57500	Menopause	627.2	Other 76815	V23.0
Endometrial Bx		58100	Menstrual irregularity	626.4	Gyn US 76830	
HSG		58340	Mittleschmirtz	625.2	**Please circle any special situations:**	
Injections	IM	90772	Mullerian anomaly			
	IV	90784	Didelphys	752.2	A consultation takes place on the	–25
IUI treatment	Natural-IUI	58322	Mullerian agenesis	752.49	day of the procedure	
	CC-IUI	58322	Sept/bico/unic:	752.3		
	FSH-IUI	58322	Ovarian cyst		A decision is made to do	–57
Sonohysterogram		58340/76831	Luteal	620.1	major surgery in 1Ð2 days	
Other Services			Follicular	620.0		
Urine pregnancy test **DX V72.4**		81025	Endometrioma	617.1	A procedure is started but can	–53
Urine analysis		81000	Unspecified	620.2	not be completed	
Specimen handling		99000	Ovarian hyperstimulation	256.9/789.67		
Wet smears		87205	Ovarian torsion	620.5	Unrelated service during surgical	–24
Paracervical block		64435	PID Ð chronic	614.9	global	

Figure 21.2 Sample fee ticket with CPT and diagnostic codes.

B. Hysterosalpingogram[a]
   81025—urine pregnancy testing
   58340—induction of dye
C. Sonohysterogram[a]
   81025—urine pregnancy testing
   76831—hysterosonography
   58340—induction of saline
D. Insemination treatments
   1. Intracervical (donor insemination)—58321
   2. Intrauterine insemination
      a. Sperm washing—58323
      b. Limited semen analysis—89310
      c. Performance of the insemination—58322
E. Injections (i.e., hCG, methotrexate)—96372

Billing for Surgical Procedures

There are several important points concerning billing for surgical procedures, which are described below. It is important that the physician work with the billing personnel to make sure the coding is done correctly.

Relative Value Units

Insurance companies base reimbursement for a procedure on the number of the Relative Value Units (RVU). The Medicare Resource Based Relative Value Scale (RBRVS) was implemented in 1992 as a means to determine physician reimbursement for services on Medicare patients, but all insurance companies have adopted it as well. The system is updated on a regular basis. The RVU is a measure of the time and intensity of the procedure that is performed. For instance, a diagnostic hysteroscopy has 7.91 RVU while a hysteroscopic resection of a uterine septum has 16.63 RVU. The number of RVU for a procedure is directly related to the level of reimbursement. If multiple procedures are performed, it is important that the primary procedure (with the most RVU) is listed first, and then all secondary procedures are listed in descending order of decreasing RVU with a modifier (–51). Generally, the primary procedure is reimbursed at 100%, and then the secondary procedures are reimbursed at a lower percentage. For a list of the current RVU, visit the Centers for Medicare and Medicaid Services (CMS) Web site http://www.cms.hhs.gov/PhysicianFeeSched/.

Bundling

Bundling is a process whereby the CPT codes of multiple procedures are combined into one. For example, a patient who underwent a hysteroscopy with a polypectomy would be assigned the CPT code 58558. During the procedure, a cervical dilation (57800), a diagnostic hysteroscopy (58120), and a D&C (58120) were performed. All of these procedures have separate CPT codes. However, these procedures cannot be separately billed because the CPT code for the operative hysteroscopy (58558) is bundled and includes these procedures. The CMS instituted a policy called the Correct Coding Initiative (CCI) to define bundling and unbundling of surgical procedures. Updates are published quarterly (http://www.cms.gov/NationalCorrectCodInitEd/01_overview.asp#TopOfPage).

Global Reimbursement

Payment for a surgical service is a global type of reimbursement that covers a period of time prior to and following the surgery. The global payment may include the time spent doing the

[a]In some cases, a paracervical block (CPT code—64435) and/or a cervical dilation (CPT code—57800) are necessary to complete these procedures. If so, these procedure codes should be submitted for reimbursement.

preoperative history and physical examination. Following the surgery, any routine follow-up care during the postoperative period (ranging from 0 to 90 days depending on the procedure) may also be included in the global period. The definition of the global period can vary depending on the surgery preformed and is defined by CMS.

Using Modifiers

Modifiers are ways to redefine a surgical procedure or an evaluation and management code under special circumstances. The use of modifiers is necessary for reimbursement for the extent of the services provided. The ACOG and the AMA coding manuals provide a description of these modifiers. There are several situations that make it necessary to use modifiers to get reimbursed. Examples of some of these situations are as follows:

- A consultation with the patient occurs on the same day of an office procedure (i.e., endometrial biopsy). (*Modifier –25*)
- An office visit takes place and a decision is made to perform the surgery that same day. (*Modifier –57*)
- The surgical procedure is more complicated and takes additional time. (*Modifier –22*)
- An open laparoscopy is performed. (*Modifier –22*)
- At the time of surgery, bilateral procedures are performed on the ovaries (or tubes). (*Modifier –50*)
- Multiple surgeries are performed on the same day. (*Modifier –51*)
- A repeat procedure is performed by the same physician within the global period. (*Modifier –76*)
- A surgical assistant (*Modifier –80*)
- A surgical assistant is used when a resident is unavailable. (*Modifier –82*)
- A procedure is started but aborted. (*Modifier –53*)

ICD-9-CM Diagnostic Codes

The CPT code for any E/M or procedure must be accompanied by a compatible diagnosis. The current system in use is the *ICD-9-CM*. Please refer to the fee ticket we use in Figure 21.2 with all of the diagnostic codes.

Note: If the patient does not have insurance coverage for infertility services, it is not appropriate to submit a diagnosis such as endometriosis or uterine fibroids to obtain reimbursement from the insurance company. One must use infertility diagnosis codes if infertility services are being provided.

Available Resources for Coding Issues

1. Publications by the American Medical Association (http://www.ama-assn.org). Call 1-800-621-8335 to order.
2. *International Classifications of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), 5th edition; published by INGENIX (1-800-464-3649)
3. American College of Obstetricians and Gynecologists (ACOG) (http://www.acog.com).
    1. OB/GYN Coding Manual
    2. *Online discussion*—CPT/ICD9 Coding and Reimbursement section—Questions can be posted and will be answered by their coding experts.
4. The American Society for Reproductive Medicine (http://www.asrm.org)—The Web site has a section titled "Coding Q&A." Questions can be posted and then are answered by their coding experts.

22 Quick reference

Box 1 Basic infertility evaluation

- CD 3-FSH, estradiol
- Hysterosalpingogram
- Semen analysis
- Preconceptional blood work
  - TSH
  - CBC
  - Blood type and screen
  - RPR
  - Antibody screens for
    - Rubella
    - Varicella
    - Hepatitis
    - HIV
  - Genetic screening (if indicated)

Box 2 Interpretation of cycle day 3 hormone levels

FSH level[a] (mIU/mL)	Estradiol level (pg/mL)	Ovarian[a] reserve
>10	<70	↓
>10	>70	↓
2–10	>70	↓
2–10	<70	Normal

[a]Cutoff value may depend on assay method.

Box 3 Clomiphene citrate challenge test

1. Cycle day 3—FSH, estradiol levels
2. Clomiphene citrate 100 mg cycle days 5–9
3. Cycle day 10—FSH level

Interpretation: If either of the FSH levels are >10 mIU/mL or the estradiol is >70 pg/mL, the test is considered abnormal and confirms reduced ovarian reserve.

Box 4 Genetic testing based on ancestral backgrounds

Ancestral group	Disease	Screening test
Caucasian, Native American	Cystic fibrosis	DNA testing
French Canadian, Cajun	Tay–Sachs	Assessment of hexosaminidase enzyme activity or DNA testing
Jewish	Canavan disease	DNA testing
	Cystic fibrosis	DNA testing
	Familial dysautonomia	DNA testing
	Tay–Sachs	Assessment of hexosaminadase enzyme activity or DNA testing
African, Asian, Cambodia, Caribbean, Central America, India, Indonesia, Laos, Malaysia, Mediterranean, Middle Eastern, Pakistan, Thailand, Turkey, Vietnam	Hemoglobinopathies	CBC, Hgb electrophoresis

Box 5 The 2011 American diabetes association (ADA) threshold glucose values

Test	Normal	Borderline	Diabetes
HgbA1C	$\leq$5.6%	5.7–6.4%	$\geq$6.5%
Fasting blood glucose[a]	<100 mg/dL	100–125 mg/dL	$\geq$126 mg/dL
2-hr blood glucose following an OGTT[b]	<140 mg/dL	140–199 mg/dL	$\geq$200 mg/dL

[a]Fasting is defined as no caloric intake for at least 8 hr.
[b]The oral glucose tolerance test (OGTT) involves a fasting blood glucose level, ingesting of 75 g anhydrous glucose dissolved in water, with another blood glucose level 2 hr later.

Box 6 Recurrent miscarriage workup

1. Rule out environmental exposures and lifestyle issues
2. Assessment of ovarian function
   - Menstrual history
   - Cycle 3—FSH, estradiol, TSH
3. Examination of uterine cavity by one of the following
   - Hysterosalpingogram
   - Sonohysterogram
   - Hysteroscopy
4. Autoimmune workup
   - Anticardiolipin antibodies
   - Lupus anticoagulant
   - Thrombophilia workup
5. Chromosomal
   - Karyotypes on both partners

Box 7 Chromosomal abnormalities in liveborn infants and maternal age[a]

Maternal age	Risk for Down's syndrome	Total risk for chromosomal anomalies[b]
20	1/1667	1/526
21	1/1667	1/526
22	1/1429	1/500
23	1/1429	1/500
24	1/1250	1/476
25	1/1250	1/476
26	1/1176	1/476
27	1/1111	1/455
28	1/1053	1/435
29	1/1000	1/417
30	1/952	1/385
31	1/909	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

[a]The data presented above were modified from Hook DB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249:2034–2038; and Hook ER. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981; 58:282–285.

[b]The other chromosomal anomalies that increase with maternal age in addition to 47,+21 (Down's syndrome) are 47,+18; and 47,+13; 47,XYY (Klinefelter's syndrome); 47,XYY and 47,XXX. The incidence of 47,XXX for women between the ages of 20 and 32 yr is not available.

Box 8 **A list of commonly used fertility medications**

Medication	Indication	Dosage	Comments
Progesterone	1. Recurrent miscarriage 2. IVF/egg donation treatment 3. Surgical removal of corpus luteum during first trimester	Vaginal - Crinone® 90 mg qd - suppositories 100 mg bid - Prometrium 100 mg tid Oral - Prometrium 100 mg tid Intramuscular - Progesterone-in-oil available in 10-cc bottles (50 mg/cc); administer 50 mg qd (1 cc) by IM injection	1. Natural progesterone medications are not associated with an increased risk of birth defects. 2. Progesterone can delay the onset of a menstrual period even if the patient is not pregnant. 3. Progesterone should be discontinued by 10 wk of pregnancy.
Clomiphene citrate	1. Anovulation 2. Unexplained infertility 3. For intrauterine insemination treatment 4. See chapter 7 for more detailed description	50–150 mg cycle days 3–7	1. Common side effects: hot flushes, visual symptoms, emotional irritability 2. Multiple pregnancy rate—10%, 9% twins 1% triplets 3. Most pregnancies are achieved after 3–4 months of treatment
Metformin	1. Chronic anovulation/polycystic ovarian disease 2. See chapter 6 for detailed description	1. Metformin is available in 500 mg tablets 2. 500 mg qd x 1 wk; then 500 mg bid x 1 wk; then 500 mg tid	1. Check renal and liver studies; fasting glucose 2. Side effects: gastrointestinal upset including diarrhea 3. See patient every 4–6 wk. Check pregnancy test if indicated 4. Discontinue metformin with the establishment of pregnancy
Dopaminergic agents Parlodel® Dostinex®	1. Hyperprolactinemia 2. See chapter 6 for a detailed description	1. Parlodel—1.25 mg qhs for 1 wk, then increase to 2.5 mg qhs 2. Dostinex—0.5 mg twice a week	1. Repeat prolactin level in 2–3 wk and adjust dose accordingly 2. Side effects: gastrointestinal upset, fatigue, dizziness, and nasal stuffiness
Dexamethasone	1. Adrenal hyperandrogenism—need to R/O Cushing's disease and adrenal tumor 2. Used in combination with clomiphene citrate 3. See chapter 6 for a detailed description	0.5 mg qhs	1. Check AM cortisol level in 1 mo if <3 μg/dL, then the dose should be decreased to 0.25 mg qhs 2. Discontinue when pregnancy is achieved

Box 9 CDC 2008 IVF statistics

Treatment	Live birth rates by age group (%)					Multiple pregnancy rate
	<35 yr	35–37 yr	38–40 yr	41–42 yr	>42yr	
IVF (± ICSI)[a]	41.4	31.7	22.3	12.6	4.2	29[b]
Frozen embryo transfer[c]	35.6	30.9	26.1	22.1	13.9	
Egg donation[c]			55.1			

[a]Live birth rates per cycle initiated.
[b]Multiple pregnancy rate: twins, 27.5%; triplets and more, 1.4%.
[c]Live birth rates per embryo transfer.

Box 10 Body mass index

	Normal						Overweight					Obesity									Extreme obesity						
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
4' 10"	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215
4' 11"	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	215	222
5' 0"	97	102	107	112	118	123	128	133	138	143	148	153	158	163	169	173	179	184	189	194	199	204	209	215	220	225	230
5' 1"	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238
5' 2"	104	109	115	120	126	131	136	142	147	153	158	164	169	174	180	185	191	196	202	207	213	218	224	229	235	240	246
5' 3"	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	192	197	203	208	214	220	225	231	237	242	248	254
5' 4"	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262
5' 5"	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270
5' 6"	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278
5' 7"	121	127	134	140	146	153	159	166	172	178	185	191	198	204	210	217	223	230	236	242	249	255	261	268	274	280	287
5' 8"	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295
5' 9"	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304
5' 10"	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313
5' 11"	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322
6' 0"	140	147	154	162	169	177	184	191	199	206	213	221	228	235	243	250	258	265	272	279	287	294	302	309	316	324	331
6' 1"	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340
6' 2"	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350
6' 3"	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359
6' 4"	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	326	339	344	353	361	369

Index

The Boston **IVF**
Handbook of Infertility
Third Edition

A practical guide for practitioners who care for infertile couples

Edited by

Steven R Bayer MD
Michael M Alper MD
Alan S Penzias MD

Boston IVF and Harvard Medical School
Boston, Massachusetts, USA

Boston IVF was established in 1986 as one of the first freestanding IVF centers in the United States, and since its inception has been a leader in the cutting-edge reproductive technologies.

This third edition of their reference text provides a coherent and structured approach to treating the infertile couple that can be of benefit to the gynecologist, the reproductive endocrinologist, and the reproductive medicine nurse.

The use of flow-diagrams and boxed summary information enables concise and easy reference to complicated data. New to this edition are chapters on polycystic ovarian syndrome, recurrent pregnancy loss, and the male patient, amongst others.

informa
healthcare

Telephone House, 69-77 Paul Street, London EC2A 4LQ, UK
52 Vanderbilt Avenue, New York, NY 10017, USA

www.informahealthcare.com
www.informahealthcarebooks.com

ISBN 978-184184810-5