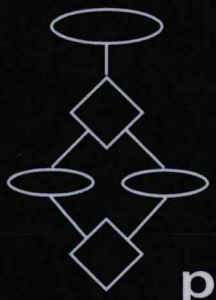

practical pathways *in*
OBSTETRICS & GYNECOLOGY

# Infertility

*Marcelle I.*
Cedars

# INFERTILITY

## PRACTICAL PATHWAYS IN OBSTETRICS & GYNECOLOGY

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**McGRAW-HILL**
*Medical Publishing Division*
New York Chicago San Francisco Lisbon London Madrid Mexico City Milan
New Delhi San Juan Seoul Singapore Sydney Toronto

The McGraw-Hill Companies

**Infertility**



1 2 3 4 5 6 7 8 9 0 DOC/DOC 0 9 8 7 6 5

ISBN 0-07-139931-3

This book was set in Melior by International Typesetting and Composition.
The editors were Andrea Seils and Michelle Watt.
The production supervisor was Richard Ruzycka.
Project management was provided by International Typesetting and Composition.
The cover designer was Mary McKeon.
RR Donnelley was printer and binder.

This book is printed on acid-free paper.

**Library of Congress Cataloging-in-Publication Data**

Infertility / [edited by] Marcelle Cedars.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-07-139931-3 (alk. paper)
1. Infertility. I. Cedars, Marcelle.
[DNLM: 1. Infertility—diagnosis. 2. Infertility—therapy. 3. Reproductive Techniques, Assisted. WP 570 I4301 2005]
RC889.I542 2005
618.1'78—dc22

2004056462

*This book is dedicated to my family, especially Daniel and Ariana, and to all those investigators and clinicians who work tirelessly to improve the care and caring of infertile couples*

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# Preface

Advances in the field of reproductive medicine and infertilility are made at an increasingly rapid rate. For those of us who care for infertile couples, our job becomes both easier and harder. Our job is made easier by the development of new, effective treatment strategies that may offer hope to our patients. However, the complexity of treatments and the significant impact these treatments may have on personal and social norms makes treatment more difficult for both our patients and ourselves. The rapid explosion in reproductive genetics is only now beginning to have its impact felt in our field. The application of this new knowledge to our field offers great promise for the future, but must be introduced after careful study and consideration.

In the chapters that follow, I have attempted to present both the history—the tried and true knowledge that guides our decision-making—and the future. As we approach patients, our approach will be increasingly multi-disciplinary. The involvement of those with expertise in genetics and psychology will be critical. And, for those in this field, our patients and society, we will increasingly involve those with expertise in ethics and the law. It is with this broad brush that I have painted a picture of current infertility care.

# Introduction

Nearly five million American women aged 15 to 44 years report difficulty or delay in achieving a live birth. The percentage of affected women has not increased despite increased public awareness of this problem. What has changed is the number of women (couples) seeking medical attention. Each year, approximately 1.3 million of these women seek medical advice or treatment. This number has increased because of significant demographic changes in our society. These include the aging of the "baby boom" generation leading to an increased size of the reproductive age population. More importantly is the change in society with more women seeking careers and delaying fertility. In fact, the number that has changed is the number of *nulligravid* women with infertility, in other words, the women who have never had a child and are now infertile. There is a false sense by many that modern reproduction can overcome *all* factors, including those associated with age.

The chief female categories of infertility are ovulatory disorders (25%) and tubal disease (20 to 25%), including endometriosis (10%). Male infertility is the primary category in approximately 25% of cases and contributes to a further 15 to 25% of the remaining cases. Infertility remains "unexplained" in up to 20% of cases. These cases are unexplained only in that our current methods do not identify a critical factor. Although recent developments have improved the effectiveness of conventional specific therapies, the overall prognosis for childbirth is not better than 50%. This can be explained by the presence of unexplained factors that persist after conventional therapy. A further reason is the limited access in many jurisdictions to artificial reproductive technologies.

Most couples are not infertile, but rather *subfertile.* This distinction is critical as there is a small chance that conception and birth may occur without treatment. The effectiveness of treatment can therefore only be determined by randomized clinical trials preferably comparing the pertinent treatment to no-treatment or placebo. A second choice for the control group would be use of a standard active treatment for the "control." Ideally, this treatment should have been confirmed previously by randomized controlled trials. Less convincing data are generated by cohort

and case series. Unfortunately, these later study designs comprise a major share of available literature in this field. This lack of convincing data regarding treatment approaches makes care of these couples even more difficult. Each treatment option has many costs: emotional, physical, and financial, oftentimes without clear documentation of success. It is thus important to evaluate and treat couples with a comprehensive approach taking into consideration expected benefits, unwanted side-effects, and costs in dollars and time.

**Time** is a critically important factor for couples seeking fertility, as the age of the female partner is the number one prognosticator for success. After age, the duration of infertility plays a large role in considering treatment options. Thus, a prompt, efficient evaluation is likely to be most beneficial to the infertile couple. Diagnostic assessment is indicated for couples attempting pregnancy and who fail to conceive following 12 or more months of regular, unprotected intercourse. This timeframe is selected since 85 to 90% of normally fertile couples conceive in this interval of time. This "delay" will thus save many couples unnecessary testing and evaluation. Earlier assessment *is* indicated in women over 35 years of age, women with irregular menstrual cycles, or those with a high risk for tubal disease and/or endometriosis. The current focus of diagnostic testing is on a limited panel of specific investigations rather than a broad screen of tests.

It is important to remember that there is, in most couples, the chance for spontaneous conception. Recent studies estimate the average prognosis for live birth without treatment at 25 to 40% during the three years after the first infertility consultation. This translates into a cycle fecundity rate of 0.7 to 1% per month. The presence of endometriosis, abnormal sperm, or tubal disease independently reduced the chance of spontaneous pregnancy and live birth by approximately 0.5 for each variable. Infertility for greater than 3 years, female age greater than 30 years, and primary infertility were important negative prognostic factors.

**Evaluation** should focus on known causes of infertility/subfertility. Hence, the first section of this text will describe normal female and male physiology and the relevant investigation of the infertile couple. Attention will be paid to recent reviews of the literature and the development of a time and cost-sensitive evaluation.

**Treatment** should be diagnosis specific, if possible. The second section of this text therefore delves more deeply into specific etiologies of infertility and appropriate diagnostic and therapeutic interventions.

**Assisted reproductive technologies (ART),** the art of taking fertilization outside the human body, deserves special consideration and will be considered in depth in the third section of the text. Although only a small percentage of all infertile couples will actually need ART, the dramatic

advances in the last quarter century (yes, Louise Brown—the first "IVF baby"—celebrated her 25th birthday in the summer of 2003) and the strong media interest have made ART a central focus for the infertile practice and for patients. ART remains the only option for some patients and the "final" option for couples who fail simpler modalities.

## Social Issues

The field of infertility is complicated by the personal and ***emotional*** nature of the desire for parenthood. Treating couples *as* couples, rather than focusing "blame" (which couples do themselves all too often) is one way in which the physician can help. It is also crucial to give accurate and fair assessments for success so that couples can make informed decisions. Psychologic support should be available to all couples and couples considering any reproduction with third parties (donors or surrogates) should be required to meet with a psychologist. There may be many times within the fertility evaluation and treatment when couples should have a discussion regarding long-term goals: to have a child to raise as their own, to have a pregnancy to share, to share genetic traits. Each of these may or may not be achieved via adoption, donor gametes, or only with further treatment. The option of child-free living should also be included in any discussion. At times couples must be advised to stop treatment if the likelihood for success is quite low. Frequently this is a very difficult time for both the patient and the physician, but fruitless treatment should be avoided.

The potential benefit relative to potential ***cost*** (financial, physical, and emotional) must all be considered. A review of 45 reports on unexplained infertility estimated the marginal costs of treatment at $7143, $15,823, and $46,391 respectively for CC/IUI, FSH/IUI, and IVF treatment compared with untreated pregnancy rates equivalent to 1.3% per month.[1] The treatment effects are generally small. Treatment may only hasten conception in those couples who would eventually conceive in any case. Given this, the high rate of multiple gestation and its incumbent medical and social risks must be considered and every attempt should be made to limit this complication. In most cases, simple treatments should be considered before complex treatment.

This field is also complicated by the many ***ethical*** boundaries that are approached. There are issues of defining "the family" and parentage, issues about "abandoned" embryos, and about how far couples and society should go to procreate. Most recently, the issue has become public as the government has faced the critically important decision of use of "disposed" embryos from IVF for creation of stem cells. The potential

for this technology is not proven but appears to be great; however, as with the restriction on funding for IVF research, politics has all too often entered into this field. The results are not always positive for patients or society at large.

Thus, in the final section of the text, we will hear from experts in psychology, law, and ethics. This is truly a field where caring for patients requires all the skills of a clinician: healing, caring, teaching, and discovering.

## Reference

1 Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, Steinkampf MP. Efficacy of treatment for unexplained infertility. *Fertil Steril* 70(2):207–213, 1998.

# Contents


| | | |
|---|---|---|
| | *Contributors* | ix |
| | Preface | xiii |
| | Introduction | xv |
| Chapter 1 | Evaluation of the Female: Ovulation<br>**Marc A. Fritz** | 1 |
| Chapter 2 | Evaluation of the Female: Tubal Function<br>**Ashim V. Kumar, Alan H. DeCherney** | 35 |
| Chapter 3 | Uterine Function/Defects<br>**Ruben Alvero, William D. Schlaff** | 49 |
| Chapter 4 | Male Factor Infertility<br>**Paul J. Turek** | 81 |
| Chapter 5 | Common Medical Conditions and Their Impact on Reproductive Function<br>**Mitchell P. Rosen, Marcelle I. Cedars** | 91 |
| Chapter 6 | Environmental Factors Affecting Fertility<br>**Bill L. Lasley, Susan E. Shideler** | 147 |
| Chapter 7 | The Psychologic Aspects of Infertility<br>**Linda D. Applegarth** | 175 |
| Chapter 8 | Medical Management of the Anovulatory Infertile Female<br>**Kenneth K. Moghadam, Michael Thomas** | 203 |
| Chapter 9 | Complications of Ovulation Induction<br>**Tracey L. Telles** | 229 |
| Chapter 10 | Surgical Management of the Infertile Female<br>**Sae H. Sohn, Danielle Lane** | 255 |
| Chapter 11 | Medical and Surgical Management of Male Infertility<br>**Paul J. Turek** | 287 |

| | | |
|---|---|---|
| Chapter 12 | Unexplained Infertility<br>**David Guzick** | 305 |
| Chapter 13 | In Vitro Fertilization<br>**Heather Hoddleston, Mark D. Hornstein** | 321 |
| Chapter 14 | The IVF Laboratory<br>**Nancy L. Bossert, Christopher J. DeJonge** | 339 |
| Chapter 15 | Assisted Reproductive Technologies: Oocyte and Embryo Cryopreservation<br>**Shehua Shen** | 361 |
| Chapter 16 | Oocyte Donation<br>**Jane I. Ruman, Mark V. Sauer** | 385 |
| Chapter 17 | New Technologies in Assisted Reproduction<br>**David Keefe** | 405 |
| Chapter 18 | Genetics and Infertility<br>**Renee A. Reijo Pera** | 435 |
| Chapter 19 | Recurrent Pregnancy Loss<br>**William H. Kutteh** | 467 |
| Chapter 20 | Legal Issues<br>**Susan L. Crockin, Karen E. Dumser** | 479 |
| Chapter 21 | Ethical Issues in Using ART: What Your Patients Need to Consider<br>**Elena Gates** | 511 |
| | Index | 527 |

# 1 Evaluation of the Female: Ovulation

Marc A. Fritz

## Introduction

Infertility may result from a wide variety of causes. One of the most important and common causes is the failure to ovulate or *anovulation*. Tests of ovulation are therefore an integral part of the evaluation of every infertile couple. Because most such tests are noninvasive and involve relatively little cost, a test of ovulation also is usually one of the first steps in the evaluation of infertility. After first documenting anovulation, the same techniques may then be used to determine the effectiveness of any ovulation induction treatment strategy.

Any of a number of different methods may be used to determine if and when ovulation occurs. All are based on one or another of the hormonal events that characterize the normal ovulatory menstrual cycle, or on the effects that those hormones have at various sites within the reproductive system. This chapter will briefly outline the characteristics and key features of the normal menstrual cycle, describe each of the tests of ovulation commonly used in clinical practice, and discuss their interpretation and potential pitfalls.

## Guiding Questions

**Does the Patient Ovulate?**

- At what interval do you have periods? How many days from the first day of one period to the first day of the next?
- How many days do you bleed?
- If you didn't have a calendar, could you predict a period was coming?

**CAN YOU DOCUMENT OVULATION?**

- What techniques are available for documentation of ovulation?
  BBT charting
  Serum progesterone
  Urinary LH monitoring
  Endometrial biopsy
  Trasvaginal ultrasound

## The Menstrual Cycle

To understand the various tests of ovulation and how and when to use and interpret them, one must first have a firm, if only very basic, understanding of the major events in the normal menstrual cycle.

**NORMAL CYCLE CHARACTERISTICS**

The follicular phase of the ovarian cycle spans the interval from onset of menses to ovulation. In general, variations in overall cycle length reflect differences in the length of the follicular phase. In normal ovulatory cycles, the follicular phase generally varies between 12 and 20 days in duration. The luteal phase of the ovarian cycle spans the interval from ovulation to onset of the next menses. In contrast to the follicular phase, the length of the luteal phase is remarkably consistent and from 13 to 15 days in duration. Cycles in which the follicular or luteal phase duration falls outside of these ranges generally are best considered abnormal.

**KEY POINT**

***Fertile cycles should fall between 25 and 35 days in length.***

To achieve optimum reproductive efficiency, menstrual cycles generally should last no less than 25 days and no more than 35 days in duration. Cycles that are shorter than 25 days in length typically exhibit either an abnormally short follicular or luteal phase and are less likely to be fertile than those of normal length. Cycles longer than 35 days in duration also decrease fertility, if only by reducing the number of opportunities to conceive within a given interval of time. The average and also most common cycle length is 28 days, but a great many normally fertile women have cycles that are slightly shorter or longer than 28 days in duration.

**THE OVARIAN CYCLE**

The stimulus for the initiation of follicular growth is unknown, but the earliest stages are independent of pituitary gonadotropin stimulation and are ongoing, even in prepubertal girls, pregnant women, and in those using oral contraceptives. Initial follicular growth occurs in a continuous series of waves that to some extent

overlap, and each wave contains a group or cohort of follicles. The cohort recruited to participate in each new menstrual cycle is that which happens, by chance, to reach the stage of development at which it first becomes sensitive to cyclic changes in the circulating concentration of follicle-stimulating hormone (FSH). As one cycle draws to a close and another begins, FSH levels rise sufficiently to support further follicular growth and development[1,2] (Fig. 1-1).

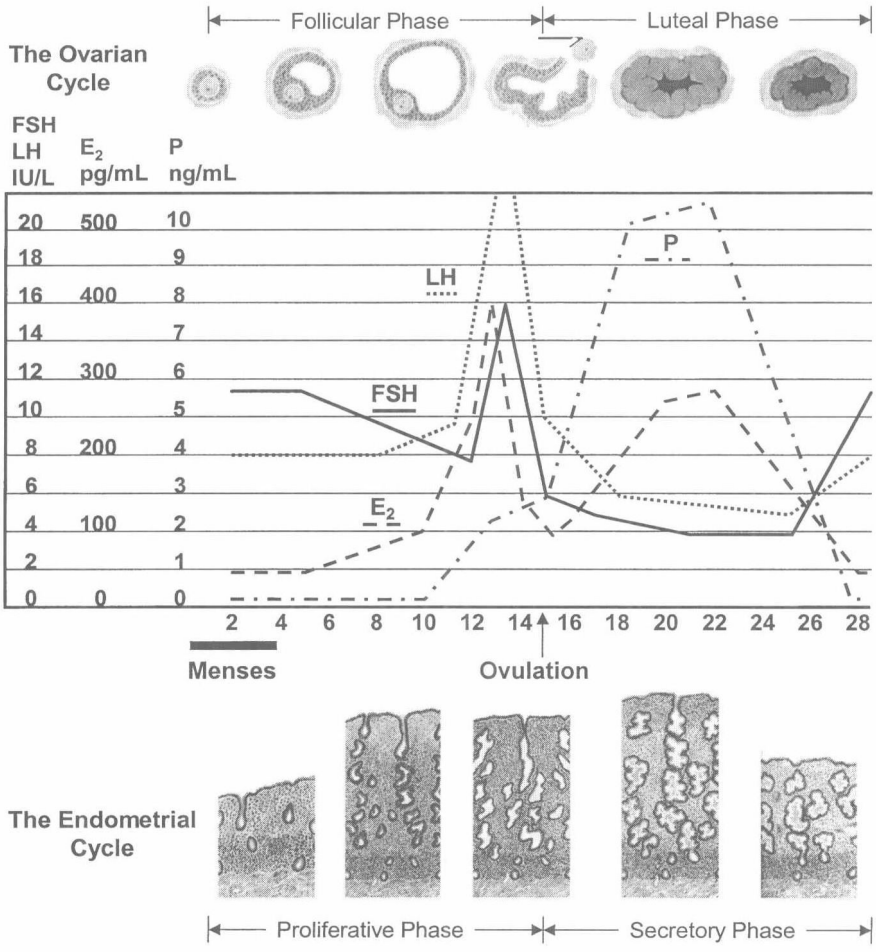


***Figure 1-1:*** The normal menstrual cycle. Temporal relationship between the cyclical changes in serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol ($E_2$), and progesterone (P) and the stages of ovarian follicular and endometrial development across the normal ovulatory menstrual cycle.