CHAPTER 22

Female Infertility

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Fertility is defined as the capacity to conceive and produce offspring. *Infertility* is the state of a diminished capacity to conceive and bear offspring. In contrast to sterility, infertility is not an irreversible state. The current clinical definition of infertility is the inability to conceive after 12 months of frequent coitus. Infertility prevalence is approximately 13% among women and 10% among men.[1] Among women and men with infertility, 57% and 53%, respectively, were reported to seek infertility treatment.[1] Women with higher income and more frequent use of the healthcare system are more likely to seek infertility treatment.[2] Among women, the prevalence of infertility increases with age. In one study, at 32 and 38 years of age, 12% and 21% of women reported infertility, respectively.[3] Since the fertility potential of the female partner decreases after 35 years of age, most authorities recommend initiating an infertility evaluation after 6 months of attempting conception in women 35 to 40 years of age and after 3 months in women over 40 years of age.[4,5] Women with known causes of infertility, such as amenorrhea, should immediately start an evaluation to assess the cause and plan the treatment.

Statistical Model of Infertility

- *The cumulative probability of conception,* F, *through month* N, *is calculated as follows:* $F = 1 - (1 - f)^N$, *where* f *is the per cycle pregnancy rate.*

The clinical definition of infertility is relatively crude because it does not reflect the wide range of fertility potential in couples that have not conceived after 12 months. The clinical definition of infertility implies the existence of a dichotomous state, either a pregnancy is achieved in 12 months and infertility is not present, or a pregnancy is not achieved in 12 months and, by definition, infertility is present. The current clinical definition of infertility is similar to analyzing a continuous variable, such as height, by using a dichotomous variable: "short" and "tall." Height is clearly much better described by a continuous measure, such as centimeters, rather than by using a dichotomous variable like "short" and "tall."

Our clinical approach to fertility and infertility would be advanced by an increased use of the statistical concept of fecundability in the fertility literature. *Fecundability* is the probability of achieving a pregnancy in one menstrual cycle. Fecundability is approximately 0.25 in healthy young couples just beginning attempts at conception. A related concept, *fecundity*, is the ability to achieve a pregnancy that results in a live birth based on attempts at conception in one menstrual cycle. Fecundability, a population estimate of the probability of achieving pregnancy in one menstrual cycle, is a valuable clinical and scientific concept because it creates a framework for the quantitative analysis of fertility potential. Based on the clinical characteristics of a population of infertile couples, the estimated fecundability may range from 0.00 in couples with an azoospermic male partner to approximately 0.04 in couples where the female partner has early stage endometriosis.

Fecundability provides a convenient quantitative estimate of the efficacy of various fertility treatments. An infertile couple with an estimated fecundability of 0.04, if left untreated, may have the choice of two approaches to the treatment of their fertility: a low-cost treatment (clomiphene plus intrauterine insemination [IUI]) that will increase fecundability to 0.08, or an expensive treatment (in vitro fertilization [IVF]) that will increase fecundability to 0.30. A clear quantitative presentation of the potential effect of each treatment on fecundability should assist the couple in choosing an optimal treatment plan. A practical problem with using fecundability as a central concept in infertility care is that the prediction models for estimating the fecundability of a couple are not well developed or validated. Factors that are important in estimating fecundability for a couple are age of the female partner, number of motile sperm, duration of subfertility, and presence of primary or secondary infertility.[6]

The concept of fecundability can be used to derive a simple statistical description of the fertility process. Fecundability *(f)* is defined as the probability of conceiving during any one cycle. The probability of failing to conceive during any one cycle is $1 - f$. Over a short period of time, the fecundability of a population is often stable.[7] For a large group of couples, the probability of conception is f for the first month, $f \times (1 - f)$ for the second month, $f \times (1 - f)^2$ for the third month, and $f \times (1 - f)^{N-1}$ for the Nth month. Using this model, the mean number of months required to achieve conception is $1/f$. The cumulative probability of conception, F, through month N is calculated as follows: $F = 1 - (1 - f)^N$. Based on this simple statistical model, assuming a normal menstrual cycle fecundability of 0.25 and starting with 100 couples, approximately 98 couples should conceive within 13 cycles. If each cycle is 28 days, then 98% of

Abstract

Infertility affects approximately 13% of women and 10% of men. The major causes of female infertility are anovulation, fallopian tube disease, pelvic adhesions, endometriosis, and unexplained infertility. Initial treatment for women with anovulatory infertility involves a sequential approach, moving from less to more resource-intensive therapies. Interventions that increase fecundability in anovulatory women include optimization of weight, letrozole or clomiphene ovulation induction for women with the polycystic ovary syndrome, and gonadotropin injections or pulsatile gonadotropin-releasing hormone (GnRH) therapy for women with functional hypothalamic amenorrhea. For women with distal tubal disease, effective treatments include in vitro fertilization (IVF) or laparoscopic tubal surgery. For couples with unexplained infertility, clomiphene plus intrauterine insemination (IUI), gonadotropin plus IUI and IVF are effective treatments. Most women who are infertile will conceive with fertility therapy.

Keywords

Anovulation
diminished ovarian reserve
tubal infertility
unexplained infertility
clomiphene
letrozole
metformin
chlamydia
hysterosalpingogram
fimbrioplasty
neosalpingostomy

couples should conceive within one calendar year (13 cycles × 28 days/cycle = 364 days).

Over a short period of follow-up, a population of couples attempting pregnancy behaves in a statistically stable manner, with a fixed proportion of the cohort becoming pregnant with each additional cycle of follow-up. As the follow-up is extended, however, the fecundability of the nonpregnant couples declines and the cumulative pregnancy rate approaches an asymptote, which is less than 100%. Conceptually, this issue can be managed by assuming that there is an asymptote to the cumulative pregnancy rate of the population, or by using complex mathematical modeling of the population fecundability based on the assumption that couples in the population have a range of per cycle pregnancy rates. This issue is of special importance in the analysis of fertility rates in populations over long periods of time, such as 2 years. This issue is of less practical importance in studies where the time period for analysis is 3 to 6 cycles.

Many studies report that the observed fecundability of a population diminishes with long-term follow-up. For example, Guttmacher[8] assessed the number of months to conception in 5574 women who achieved pregnancy between 1946 and 1956. During the first 3 months of observation, the fecundability was 0.25. During the next 9 months of observation, the fecundability was 0.15.[9] Zinaman et al. studied 200 healthy couples who wanted to conceive. During the first 3 months of observation, the fecundability was 0.25. During the next 9 months of observation, the fecundability was 0.11 (Table 22.1). Other investigators have reported similar results.[10]

The decrease in fecundability with time suggests that each large population consists of a heterogeneous mixture of couples. Some couples have completely normal fertility and achieve pregnancy at a high rate (0.25 per cycle). The remaining couples have a lower fecundability (ranging from 0.00 to 0.15). Some of the couples in this pool will eventually present to a clinician for the treatment of infertility. At the end of 12 months of attempting conception, the couples that have not achieved conception have a fecundability in the range of 0.00 to 0.04 if left untreated (see Table 22.1).

Table 22.1 Observational Studies Often Demonstrate That the Fecundability of the Cohort Decreases as Follow-up Progresses

Cycle	Number of Women Available for Study at Start of Cycle	Number of Pregnancies in Cycle	Per-Cycle Pregnancy Rate
1	200	59	0.30
2	137	41	0.30
3	95	16	0.17
4	78	12	0.15
5	66	14	0.21
6	52	4	0.08
7	48	5	0.10
8	43	3	0.07
9	40	2	0.05
10	38	1	0.03
11	37	2	0.05
12	35	1	0.03

From Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG: Estimates of human fertility and pregnancy loss. *Fertil Steril* 65:503–509, 1996.

Successful interventions to improve fertility must increase the per-cycle pregnancy rate over the spontaneous pregnancy rate.

Unfortunately, not all pregnancies produce a live birth. Many pregnancies are lost soon after implantation. The terms occult pregnancy and chemical pregnancy are often used to describe these early pregnancy losses. *Occult pregnancy* was defined by Bloch[11] as a pregnancy that terminates so soon after implantation that there was no clinical suspicion of its existence. In one recent study, approximately 13% of pregnancies were occult.[11] Unlike occult pregnancies, a *chemical pregnancy* typically occurs in the presence of a clinical suspicion that a pregnancy may exist. A blood or urine human chorionic gonadotropin (hCG) assay demonstrates the presence of a pregnancy, but no clinical evidence of the pregnancy is detectable by ultrasound. Of all clinical pregnancies, approximately 20% result in a spontaneous abortion. Of all pregnancies, approximately 30% are lost—either as occult, chemical, or clinical spontaneous abortions (Table 22.2).[9] Women older than 40 years of age who become pregnant have a spontaneous abortion rate more than double that observed in women younger than 30 years of age.[12]

Diseases Associated With Infertility

- *The most common causes of female infertility are anovulation, tubal disease, pelvic adhesions, and endometriosis. Many couples do not have an identifiable cause of infertility, and this condition is referred to as unexplained infertility.*

Pregnancy is the result of the successful completion of a complex series of physiological events occurring in both the male and female that allows for the implantation of an embryo in the endometrium (Fig. 22.1). At a minimum, pregnancy requires ovulation and the production of a competent oocyte, production of competent sperm, proximity of the sperm and oocyte in the reproductive tract, transport of the embryo into the uterine cavity, and implantation of the embryo into the endometrium.

Some diseases, such as those that cause azoospermia, clearly have a *cause-effect relationship* with infertility. For other disease processes, such as stage I endometriosis, there is no clear cause-effect relationship between the disease and the infertile state. In these situations, it is preferable to state that there is an *association* between the disease condition

Table 22.2 Pregnancy Occurrence and Outcome During Three Consecutive Menstrual Cycles in 200 Healthy Couples Desiring Pregnancy

	Cycle Numbers			
Cycle Outcome	1	2	3	Total
Not pregnant at start of cycle	200	137	95	
Pregnant during cycle	59	41	16	116
Chemical pregnancy	7	7	1	15
Spontaneous abortion	12	5	4	21
Live births	40	29	10	79
Dropped out, not pregnant	4	1	1	6
Lost to follow-up			1	

Age of female partner, 30.6 ± 3.3 (mean ± standard deviation).
From Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG: Estimates of human fertility and pregnancy loss. *Fertil Steril* 65:503–509, 1996.

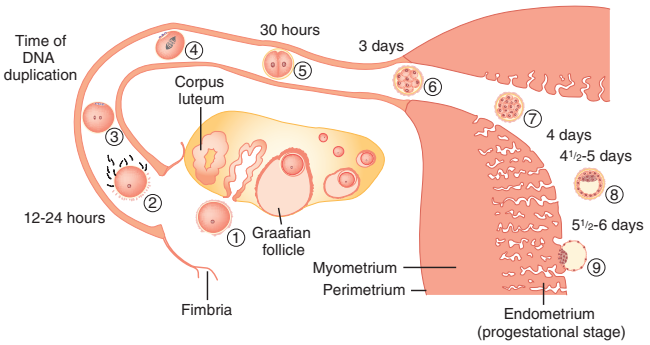

FIGURE 22.1 Schematic representation of the transport of the oocyte, sperm, and embryo in the female reproductive tract.

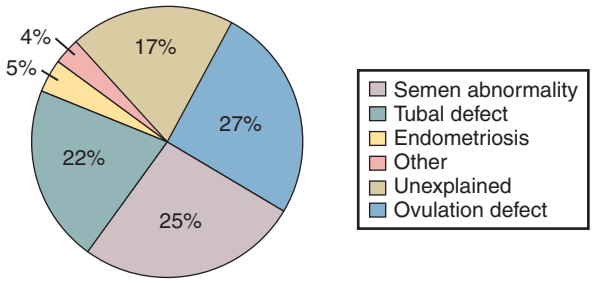

FIGURE 22.2 Primary clinical diagnoses in infertile couples. *(From Collins JA: Unexplained infertility. In: Keye WE, Chang RJ, Rebar RW, Soules MR, editors:* Infertility: evaluation and treatment. *Philadelphia, 1995, WB Saunders, p 250, with permission.)*

and the infertile state, but that causality has not been definitively established. Due to the limits of our current understanding of fertility in humans, it is often difficult to categorize disease conditions as either causing infertility (e.g., azoospermia) or associated with infertility (e.g., stage I endometriosis). Consequently, a discussion of the distribution of reproductive diseases that are diagnosed in infertile couples is not necessarily based on hard scientific data, but rather descriptive observations and assumptions about diseases that *cause* or might be *associated* with infertility.

Most tabulations of the medical conditions that "cause" infertility divide the problem into male factors and female factors. The World Health Organization (WHO) task force on Diagnosis and Treatment of Infertility conducted a study of 8500 infertile couples using a standardized diagnostic protocol.[13] In developed countries, diseases that were identified as contributing to the infertile state were attributed to the female partner in 37% of couples, to the male partner in 8% of couples, and to both partners in 35% of couples. Five percent of the couples had no identifiable cause of infertility (unexplained infertility) and 15% of the couples became pregnant during the investigation. The diseases in the female most often identified were ovulatory disorders (25%), unexplained infertility (20%), endometriosis (15%), pelvic adhesions (12%), tubal occlusion (11%), other tubal abnormalities (11%), and hyperprolactinemia (7%).

In a review of 21 published reports containing a total of 14,141 infertile couples, Collins[14] reported that the primary diagnoses in the couples were: ovulatory disorders (27%), abnormal semen parameter (25%), tubal defect (22%), unexplained (17%), endometriosis (5%), and other causes (4%), as shown in Fig. 22.2. In another data set of 2198 infertile couples, the distribution of primary diagnoses was unexplained (26%), abnormal semen parameter (24%), tubal disease (23%), ovulatory disorders (18%), endometriosis (6%), and other (3%).[15] These observations can be broadly grouped into five major conditions that influence fecundability:

1. Abnormalities in the production of a competent oocyte (anovulation, depletion of the oocyte pool, or poor oocyte function/quality)
2. Abnormalities in reproductive tract transport of the sperm, oocyte, and embryo (tubal, uterine, cervical, and peritoneal factors)
3. Abnormalities in the implantation process, including early defects in embryo development and embryo-endometrial interaction (embryo-endometrial factors)
4. Abnormalities of sperm production (male factor)
5. Other conditions, including immunological factors that can affect multiple components of the process

The initial infertility evaluation focuses on these five major processes (Box 22.1). Abnormalities of embryo-endometrial interaction are reviewed in Chapter 9. Male infertility is reviewed in Chapter 23.

Box 22.1 Initial Laboratory Approach to the Infertile Couple

PRIMARY TESTS FOR INFERTILITY

Documentation of competent ovulation
- Midluteal progesterone >3 ng/mL
- Day 3 follicle-stimulating hormone or clomiphene challenge test (if female partner >35 years old)

Semen analysis
- Volume ≥1.5 mL
- Concentration ≥15 million/mL
- Motility ≥32%
- Morphology ≥4% (using "strict" criteria)
- Terminology used to describe abnormal semen analysis: low sperm concentration, oligospermia; low sperm motility, asthenospermia; sperm morphology abnormal, teratospermia; elevated white blood cells, leukocytospermia

Documentation of tubal patency
- Hysterosalpingogram or hysterosalpingo-contrast sonography
- Assessment of the uterine cavity
- Hysterosalpingogram, hysterosalpingo-contrast sonography, or hysteroscopy

SECONDARY TESTS FOR INFERTILITY

Laparoscopy
Hysteroscopy

Initial Infertility Evaluation

◆ *Three tests should be completed early in the infertility evaluation: semen analysis, documentation of ovulation, and a test of tubal patency.*

The standard components of the infertility evaluation include a thorough history and physical examination (Table 22.3), a semen analysis (see Box 22.1), documentation of competent ovulation, documentation of female reproductive tract and tubal patency, and assessment of the uterine cavity.[16] The evaluation of the semen analysis is discussed

Table 22.3 History and Physical Examination Findings Relevant to the Infertility Evaluation in the Female Partner

History	Physical Exam Findings
Duration of infertility and results of previous tests and treatments Prior pregnancies and outcomes Pubertal milestones: adrenarche, thelarche, and menarche Menstrual cycle history from menarche to present Evidence for cycle irregularity Previous gynecological and abdominal surgery Past contraceptive use Coital frequency and sexual function Relevant medical history of male partner Current medications and allergies History of hirsutism, pelvic or abdominal pain, dyspareunia, thyroid disease, galactorrhea Current occupation and exposure to environmental toxins Use of tobacco, alcohol, and drugs Exercise history and current pattern of exercise History of stress, anxiety, depression	Weight, height, body mass index Evidence for hirsutism, acanthosis nigricans Thyroid size Presence of thyroid nodules Breast exam including palpation for breast masses and expression of nipple secretion Tanner stage of the breasts Assessment of the anatomy of the clitoris, hymenal ring, vagina, and cervix Assess for a vaginal septum Assess for cervical stenosis or displacement of cervix from midline Examination of position of the uterus and uterine size and mobility Examination of adnexae for a mass or tenderness Examination of the uterosacral ligaments and cul de sac

in Chapter 23, Male Infertility. As discussed in more detail later, ovulation may be presumptively detected based on a history of regular menses every 28 days or observation of a luteinizing hormone (LH) surge in the urine using an immunochemical method, and definitively diagnosed by a serum progesterone greater than 3 ng/mL or the histological demonstration of secretory changes on an endometrial biopsy. For women ≥35 years of age, a test of the size of the ovarian follicle pool, also known as ovarian reserve, is warranted. Tests to assess the ovarian follicle pool include measurement of (1) anti-müllerian hormone (AMH), (2) follicle-stimulating hormone (FSH) and estradiol on menstrual cycle day 3, (3) ovarian antral follicle count (AFC) by ultrasound, and (4) FSH and estradiol on cycle days 3 and 10 of a clomiphene citrate challenge test (CCCT).

Documentation of tubal patency should be accomplished early in the infertility evaluation by a hysterosalpingogram (HSG), a hysterosalpingo-contrast sonogram (HyCoSy), or a laparoscopy. Detection of uterine abnormalities can be accomplished by an HSG, HyCoSy, or hysteroscopy. An HSG has high sensitivity and few false positives for the detection of distal tubal disease, but it is associated with an approximately 15% false-positive rate for diagnosis of proximal tubal occlusion.[17] This means that if the HSG demonstrates that there is proximal tubal blockage, the finding should be confirmed by a second test (selective interventional radiology catheterization of each tube, hysteroscopic cannulation, or laparoscopy with tubal lavage). The HSG also provides evidence of the shape of the uterine cavity and will identify large intrauterine defects. As noted later (anatomical factors in the female), the HyCoSy is gaining in popularity as an initial test in the fertility work-up because it can detect tubal occlusion and is very sensitive for identifying small defects in the uterine cavity.[18,19] For the detection of uterine abnormalities, hysteroscopy remains the gold standard.[20]

Infertility tests that are probably not needed as part of the initial infertility evaluation include the postcoital test, an endometrial biopsy to detect luteal phase dysfunction, the hamster egg human sperm penetration test, a routine *Mycoplasma* culture, and antisperm antibody testing. A major problem with the postcoital test is that it has low reproducibility, low interobserver reliability, and has not been reliably shown to help guide treatment recommendations.[21-23] In addition, there is little consensus on what constitutes an abnormal postcoital test. Given these limitations, there is little scientific rationale for performing a postcoital test.

The endometrial biopsy is abnormal in many infertile women, and in the past, clinicians believed that it was the gold standard for documenting ovulation and assessing endometrial competence for implantation. However, studies have demonstrated that the rate of abnormal out-of-phase endometrial histology is similar in fertile and infertile women.[24] Given the weak correlation between abnormal (out-of-phase) biopsies and fertility, most clinicians are not performing endometrial biopsy as a first-line fertility diagnostic test.

Prior to attempting pregnancy, women should complete preconception testing, including measurement of antibody titers against the rubella, varicella, hepatitis B, and human immunodeficiency (HIV) viruses, a complete blood count to assess for hemoglobinopathies, and appropriate genetic testing. Women considering pregnancy should start a folic acid supplement to reduce the risk of birth defects, including spina bifida, and receive an influenza vaccination.[25]

Abnormalities in Oocyte Production

Disorders of oocyte production are a common cause of female infertility. The most common disorders of oocyte production are anovulation, oligoovulation, depletion of the follicle pool, and aging of the ovarian follicle resulting in poor oocyte quality. Depletion of the follicle pool and aging of ovarian follicles is associated with poor oocyte function. The term *diminished ovarian reserve* is often used to describe this situation. Anovulation is typically associated with amenorrhea or severe oligomenorrhea. Oligoovulation is typically associated with oligomenorrhea (cycle lengths >35 days). A depleted ovarian follicle pool is usually detected by the measurement of AMH, FSH, and estradiol on day 3 of the menstrual cycle, ovarian AFC by ultrasound, and/or measurement of FSH and estradiol during a CCCT. Oocyte quality is difficult to assess. Poor oocyte quality should be suspected when the age of the female partner is older than 40 years, even if tests of the ovarian follicle pool indicate good ovarian reserve.[26]

Women who have monthly menses and report moliminal symptoms—such as breast tenderness and dysmenorrhea—are typically ovulatory.[27] In low-resource settings, the basal body temperature (BBT) measurement can be used to identify ovulation. For most women, the morning basal temperature obtained prior to rising from bed is less than 98°F before

ovulation and over 98°F after ovulation. Progesterone production from the ovary appears to raise the hypothalamic set point for basal temperature by approximately 0.6°F. The temperature rise occurs 1 or 2 days following ovulation. The normal luteal phase is typically associated with a temperature rise, above 98°F, for at least 10 days in length. Occasionally BBT recordings may appear monophasic even in the presence of ovulation. A biphasic pattern is almost always associated with ovulation. If the pattern is biphasic, coitus can be recommended every other day for a period including the 5 days prior to and the day of ovulation (Fig. 22.3).[28] In most developed countries, sequential daily home measurement of urine LH in the periovulatory interval is the most common approach to detecting impending ovulation. A surge in urine LH is detected 1 or 2 days before ovulation.

A serum progesterone level greater than 3 ng/mL is diagnostic of ovulation. In the midluteal and late-luteal phase, progesterone secretion is pulsatile due to the pulsatile nature of luteinizing (LH) secretion.[29] At a conceptual level, the pulsatile nature of progesterone secretion may make it difficult to reliably use a single progesterone measurement as a marker for the adequacy of ovulation. However, in most clinical situations, a single midluteal progesterone measurement appears to be a useful marker of the adequacy of ovulation. Hull et al. have suggested that a midluteal progesterone concentration less than 10 ng/mL is associated with a lower per-cycle pregnancy rate than progesterone levels above 10 ng/mL.[30]

An endometrial biopsy with histological secretory changes is a definitive test demonstrating ovulation (see Chapter 9). Although not currently used in the infertility evaluation, it is likely that in the future the endometrial biopsy will be used to detect endometrial proteins that serve as useful markers of endometrial receptivity for implantation. Validation of the detection of implantation markers in endometrial biopsy specimens awaits future research.[31]

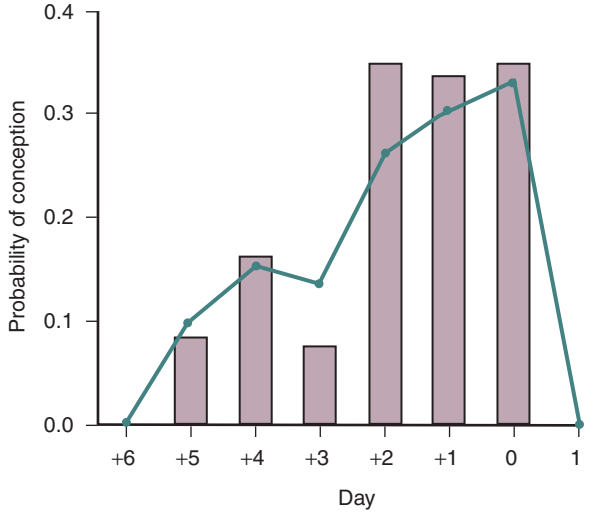

FIGURE 22.3 Probability of conception on specific days near the day of ovulation. The *bars* represent data reported by 129 women who had sexual intercourse on only 1 day in the 6-day interval ending on the day of ovulation *(day 0)*. The *solid line* shows the probability of conception based on a statistical analysis of data from 625 cycles. *(From Wilcox AJ, Weinberg CR, Baird DD: Timing of sexual intercourse in relation to ovulation.* N Engl J Med *333:1517–1521, 1995, with permission.)*

Sonographic examination of the ovary and serial measurement of urine LH or estrone-3-glucuronide can be used to demonstrate the growth of a dominant follicle, which is a necessary precondition to ovulation.[32] During menses, the follicles in the ovary are approximately 4 to 9 mm in diameter. Prior to ovulation, the dominant follicle reaches a diameter in the range of 20 to 25 mm. Demonstration of follicle growth and rupture of the dominant follicle is presumptive evidence that ovulation has occurred. Ovulation typically occurs about 36 to 44 hours after the onset of the urine LH surge, and approximately 24 hours after the urine LH peak. In one large prospective study, the detection of a urine LH surge by patients using a home detection kit was associated with ovulation as demonstrated by a secretory endometrial biopsy in 93% of cycles.[33]

Many diseases can cause anovulatory infertility. The most common causes of adult-onset anovulation are hypothalamic dysfunction (35% of cases), pituitary disease (15%), and ovarian dysfunction (50%).[34,35] The most common causes of hypothalamic dysfunction are abnormalities in weight and body composition, stress, and strenuous exercise (see Chapters 18 and 19). Less common causes of hypothalamic dysfunction are infiltrating diseases of the hypothalamus, such as lymphoma and histiocytosis. The pituitary disorders that cause anovulation (see Chapters 3 and 20) are prolactinoma, empty sella syndrome, Sheehan syndrome, Cushing disease, acromegaly, and other pituitary tumors. The most common ovarian causes of anovulation are ovarian failure (depletion of the oocyte pool) and ovarian hyperandrogenism (e.g., polycystic ovary syndrome [PCOS]). Occasionally, thyroid disease can be associated with anovulation.

Evaluation of the various causes of anovulation can be complex. Typically, measurement of body weight and height, and measurement of serum FSH, prolactin, thyroid-stimulating hormone (TSH), and androgens, if indicated, can help identify the cause of the anovulation. A progestin withdrawal test may be helpful to evaluate the degree of hypogonadism present, and may help guide treatment choices.

Patients with anovulation have the greatest success with infertility therapy (see Chapter 30). Treatment of anovulatory disorders can result in fecundability similar to that observed in normal couples (0.15 to 0.25). The choice of treatment is dependent upon the cause of the anovulation. Common treatment choices include:

1. Interventions to modulate weight
2. Letrozole
3. Clomiphene citrate (CC)
4. Clomiphene plus other hormone adjuvants
5. Gonadotropin treatment (see Chapter 30)
6. Ovarian surgery
7. Pulsatile administration of GnRH
8. Bromocriptine and cabergoline

Interventions to Modulate Weight and Induce Ovulation

◆ *Many obese anovulatory infertile women can achieve pregnancy by lifestyle changes including calorie restriction and moderate exercise. Many excessively lean anovulatory infertile women can achieve pregnancy by gaining weight, especially by increasing body fat.*

Anovulation, oligoovulation, and subfertility are commonly observed in women above or below their ideal body weight (see also Chapter 18).[36] In one study of 597 cases of women with anovulatory infertility and 1695 fertile controls, overweight women (body mass index [BMI] >27 kg/m^2) had a relative risk (RR) of anovulatory infertility of 3.1 compared with women of BMI 20 to 25 kg/m^2. Excessively thin women with a BMI less than 17 kg/m^2 had an RR of anovulatory infertility of 1.6. The investigators concluded that the risk of ovulatory infertility is highest in overweight women, but is also increased in underweight women.[37] For women who are far below or far above their ideal body weight, appropriate management of dietary intake may be associated with resumption of ovulation and pregnancy.[38] For example, Pasquali et al.[39] demonstrated that anovulation in obese women with PCOS could be successfully treated with weight loss. Obese women with anovulation and PCOS were placed on a 1000- to 1500-calorie diet for 6 months. The mean weight loss was 10 kg. After weight loss there was a 45% decrease in basal LH concentration and a 35% decrease in serum testosterone. Many women in this study became pregnant. Most studies of the impact of weight loss on reproductive function did not include a control group. Guzick et al. reported the results of a randomized, controlled trial of the impact of weight loss on reproductive function.[40] Twelve obese, hyperandrogenic, oligoovulatory women were randomized to either a weight reduction program or a "waiting list" observation control group. The six women randomized to the weight reduction program had a mean decrease in weight of 16 kg, a significant decrease in circulating testosterone, a decrease in fasting insulin, and no change in LH pulse frequency and amplitude. In the women who were randomized to the weight reduction program, four of six resumed ovulation. All of the women in the control group who were anovulatory before the study remained anovulatory during the study.

Elevated BMI and sedentary lifestyle decrease fecundability (see Chapter 18). Weight loss and a modest increase activity can increase fertility potential. In one study 574 infertile women with a BMI of 29 kg/m^2 or more (median BMI of 36 kg/m^2) were randomized to receive a 6-month lifestyle intervention or to a control group. The lifestyle intervention included a reduction in calorie intake by 600 kcal daily with the goal of reducing body weight by ≥5% and increased activity including 10,000 steps daily plus 30 minutes of moderate exercise 2 to 3 times weekly. Natural conception was achieved by 26% of the women in the lifestyle intervention and 16% of the women in the control group (RR 1.61; 95% confidence interval [CI], 1.16 to 2.24).[41] Weight loss prior to ovulation induction may result in a greater live birth rate in women with PCOS.[42] Overweight and obesity are associated with an increased risk of spontaneous abortion and fetal loss, making normalization of weight an important prepregnancy goal.[43,44]

Weight loss is difficult to achieve. Consultation with a nutritionist, encouragement by a physician, a hypocaloric diet, and initiation of an exercise program may be the most effective nonsurgical interventions that can help a woman lose weight. Surgical methods of weight reduction can be very effective, especially in women with a BMI over 40 kg/m^2.[45]

Excessively lean women are at increased risk for anovulatory infertility. In experimental models, oligoovulation ensues following interventions that result in daily energy expenditure greater than daily calorie intake. In the captive female monkey, regular ovulatory cycles are observed with routine activity and a steady calorie intake at 300 kcal daily. When calorie intake is maintained at 300 kcal daily, but activity is increased to include 6 miles of additional ambulation daily, anovulation and amenorrhea ensue. Increasing calorie intake to up to 600 kcal daily while maintaining 6 miles of exercise daily results in resumption of ovulation and menses. In the exercising monkey, resumption of ovulation also can be initiated without an increase in calorie intake by administering pulses of GnRH.[46] In a study of sedentary women assigned to exercise plus calorie restriction or exercise plus a eucaloric diet, the exercise plus calorie restriction group produced greater declines in ovarian steroid production than exercise plus a eucaloric diet.[47]

Hormones that help the brain assess the relative levels of calorie intake and energy expenditure include leptin, insulin, thyroid hormones (thyroxine and triiodothyronine), growth hormone, insulin-like growth factor 1 (IGF1), cholecystokinin, glucagon-like peptide-1, and ghrelin. Women with hypothalamic amenorrhea (hypothalamic hypogonadism) often have low levels of leptin. Two clinical trials reported that the administration of exogenous leptin or a leptin decapeptide (metreleptin) to lean women with hypothalamic amenorrhea resulted in the resumption of ovulatory menses in some of the subjects.[48,49] In addition, metreleptin administration for 36 weeks increased free triiodothyronine, IGF1, and osteocalcin. Leptin may exert its effect on GnRH secretion by a direct action on kisspeptin-releasing neurons.[50]

Lean women with anovulatory infertility are often reluctant to gain weight, alter their diet, or reduce their exercise regimen. However, in one study of 26 underweight women who practiced strict dieting and were infertile, the subjects were counseled by a dietician and given physician-directed advice to increase their BMI. After the intervention, the women gained a mean of 3.7 kg and 73% of the women became pregnant.[51] Interpersonal psychodynamic psychotherapy or cognitive behavior therapy may help lean anovulatory women to resume ovulation.[52] It is important to try to achieve a normal BMI prior to initiating ovulation induction in excessively lean anovulatory women because in a pregnant woman with a low BMI there is an increased risk of delivering an infant with low birth weight, small head circumference, and microcephaly.[53]

Specific dietary factors may influence the risk of anovulatory infertility. For example, in one prospective study, women who consumed iron supplements were reported to have a 40% lower risk of anovulatory infertility.[54] In another prospective study, dietary patterns characterized by high consumption of monounsaturated rather than trans fats, vegetable rather than animal protein, low glycemic carbohydrates, high fat dairy, and multivitamins were associated with a reduced risk of ovulatory infertility.[55] For lean or normal-weight anovulatory infertile women, one practical recommendation for increasing high fat dairy intake is to eat ice cream and put butter on their vegetables. Myo-inositol is a dietary supplement that is a precursor of D-chiro-inositol, which is involved in the control of glucose metabolism and cell response to insulin stimulation. In one small observational study without a control group, oligoovulatory women with PCOS who took myo-inositol, 2 g twice daily, reported an increase in spontaneous

menstrual cycles. Forty percent of the subjects became pregnant during 6 months of myo-inositol treatment.[56]

Letrozole

- *For the treatment of anovulatory infertility caused by PCOS, letrozole is gradually replacing clomiphene as the first-line treatment.*

Aromatase inhibitors, including letrozole and anastrozole, block estradiol synthesis, reduce estradiol feedback on the hypothalamus-pituitary, and increase production of FSH in women with PCOS. Letrozole at doses of 2.5 to 7.5 mg daily for 5 days, and anastrozole at a dose of 1 mg daily for 5 days have been demonstrated to induce ovulation in women with PCOS. In addition, clinical trials have reported that letrozole is superior to clomiphene for ovulation induction, but anastrazole is NOT superior to clomiphene. These data suggest that letrozole may be a first-line treatment for anovulatory infertility due to PCOS, but anastrozole should generally not be used for this indication. The US Food and Drug Administration (FDA) has approved letrozole for the treatment of breast cancer in postmenopausal women, but it is not approved for ovulation induction. Infertile women using letrozole for ovulation induction should be aware of the off-label use of letrozole.

Legro et al. randomized 750 women with anovulatory infertility and PCOS to clomiphene or letrozole for ovulation induction.[57] The medications were used in a step-wise dose escalation protocol. The doses of clomiphene were 50, 100, and 150 mg/day. The doses of letrozole were 2.5, 5, and 7.5 mg/day. The lowest dose that induced ovulation as determined by the measurement of progesterone was used in up to 5 cycles. The medications were given for 5 days on cycle days 3 to 7 following a spontaneous menses or a medroxyprogesterone acetate withdrawal bleed. The ovulation rates for letrozole and clomiphene were 62% and 48%, respectively ($P < .001$). The live birth rates for letrozole and clomiphene were 28% and 19%, respectively ($P < .007$). Among women with a BMI of ≤30.3 kg/m^2, both letrozole and clomiphene resulted in a similar live birth rate, 35% and 30%, respectively. Among women with a BMI ≥30.3 kg/m^2, the live birth rates with letrozole and clomiphene were 20% and 10%, respectively. For letrozole and clomiphene, the spontaneous abortion rate (32% and 29%) and the twinning rate (3.4% and 7.4%) were not statistically different. These results demonstrate the critical importance of achieving a BMI less than 30 kg/m^2 prior to ovulation induction. This study also indicates that letrozole is superior to clomiphene for ovulation induction in PCOS, especially in women with a BMI ≥30.3 kg/m^2.

In contrast to letrozole, anastrozole is not superior to clomiphene. In clinical trials, anastrozole at doses of 1, 5, and 10 mg daily for 5 days was less effective for ovulation induction in the first cycle of treatment than clomiphene at a dose of 50 mg.[58,59]

Letrozole and anastrozole are not approved by the FDA for ovulation induction. Pregnancy and birth registries indicate that pregnancy outcome following ovulation induction with aromatase inhibitors is good.[60] In one registry, the risk of congenital cardiac malformations was greater with clomiphene-induced pregnancy than with letrozole-induced pregnancy.[61] However, concern remains about the potential adverse effects of these agents on pregnancy, especially given the known adverse effects of aromatase inhibitors on rabbit and rodent pregnancies.

Ovulation induction and ovarian stimulation in women with estrogen-sensitive tumors, such as breast cancer, may be a special situation where the use of aromatase inhibitors should be prioritized.[62] Aromatase inhibitors increase FSH levels, but block estradiol production, resulting in folliculogenesis with relatively reduced levels of circulating estradiol compared with clomiphene or gonadotropin treatment. In women with a history of estrogen-sensitive tumors, inducing folliculogenesis and ovulation while maintaining relatively low levels of circulating estradiol has a theoretical advantage.[63] This effect may be especially advantageous in women with a history of breast cancer planning on undergoing an IVF cycle.[64]

Aromatase inhibitors may be an effective monotherapy option for women who are clomiphene resistant. In one trial, 250 anovulatory women with PCOS who did not ovulate with standard doses of clomiphene were randomized to treatment with letrozole 2.5 mg daily for 5 days or metformin 1500 mg plus clomiphene 150 mg daily for 5 days. The ovulation rate was 65% in the letrozole group and 70% in the metformin-clomiphene group.[65] The pregnancy rate was 15% and 14% in the letrozole and metformin-clomiphene groups, respectively.[65] Given the superiority of letrozole compared to clomiphene or anastrozole, first-line therapy with letrozole is recognized as a reasonable option, even though it is not FDA approved for this purpose.[66]

Clomiphene

- *Many anovulatory women with PCOS do not become pregnant on clomiphene, and the use of alternative agents such as letrozole, or adjuvants such as glucocorticoids or metformin, should be considered if 3 cycles of clomiphene with escalating doses does not result in ovulation.*

Clomiphene, a nonsteroidal triphenylethylene derivative estrogen agonist-antagonist related to tamoxifen and diethylstilbestrol, was first synthesized in 1956. In 1961, Greenblatt et al.[67] reported clomiphene to be effective in the induction of ovulation, and the drug was approved by the FDA in 1967 (see also Chapter 30). CC is marketed as a racemic mixture of enclomiphene *(E, trans)* and zuclomiphene *(Z, cis)* in a ratio of approximately 3 to 2. The Z-isomer may have greater ovulation-inducing properties than the *trans* isomer. An important recent observation is that nonsteroidal triphenylethylene compounds like tamoxifen and clomiphene may require bioactivation by the liver cytochrome P450 enzyme 2D6. In one study, liver microsomes containing *CYP2D6*, metabolized clomiphene to two potent estrogen antagonist compounds, *(E)*-4-hydroxyclomiphene and *(E)*-4-hydroxy-*N*-desethylclomiphene.[68] These two compounds demonstrated 50% inhibition of estrogen receptor function at concentrations of 2.5 and 1.4 nM, respectively. The activity of *CYP2D6* shows significant variation among women, suggesting that allelic variation in this enzyme may contribute to the variability in the response to clomiphene.

Clomiphene has a half-life of approximately 5 days. It is metabolized by the liver and excreted in the feces. Fecal

clomiphene can be detected up to 6 weeks after discontinuing the drug. In *normally cycling women*, the administration of CC, 150 mg daily for 3 days, resulted in an increase in the serum concentration of LH and FSH of 40% and 50%, respectively.[69] In addition, LH pulse frequency increased from 3.3 to 6.8 pulses per 8 hours. The clomiphene-induced increase in LH pulse frequency indicates that clomiphene has an action at the hypothalamus. In women with PCOS who already have a high LH pulse frequency, clomiphene does not further increase LH pulse frequency, but it does increase LH pulse amplitude and serum levels of LH and FSH.[70] Successful induction of ovulation with clomiphene requires an intact hypothalamic-pituitary-ovarian axis. In contrast, exogenous gonadotropin treatment is effective even in the absence of a functional hypothalamus or pituitary.

Evidence that clomiphene has central nervous system effects includes the observation that clomiphene induces vasomotor symptoms,[71] increases LH pulse frequency, and partially blocks the contraceptive potency of estrogen.[72] Studies in laboratory animals demonstrate that clomiphene can decrease estrogen-stimulated hypothalamic tyrosine hydroxylase,[73] and that clomiphene increases GnRH secretion from the rat medial basal hypothalamus.[74]

In addition to a hypothalamic site of action, clomiphene also has biologic effects on the pituitary, ovary, endometrium, and cervix. In incubations of rat pituitary cells, both estradiol and clomiphene augmented GnRH-induced release of FSH and LH. Zhuang et al.[75] demonstrated that clomiphene, estradiol, and diethylstilbestrol all augmented gonadotropin induction of aromatase activity in rat granulosa cells. In hypoestrogenic women receiving exogenous estrogen, clomiphene can cause endometrial atrophy.[76] Clomiphene can diminish estrogen-induced cervical mucus quantity and quality, as demonstrated by decreased ferning and spinnbarkeit formation.[77,78] Although clomiphene may induce ovulation, the adverse effects of on the endometrium and cervix may reduce the pregnancy rate per ovulatory cycle.

Clomiphene is most effective in inducing ovulation in women with euestrogenic anovulation, including women with PCOS. In women with severe hypoestrogenism and hypogonadotropic hypogonadism, clomiphene is typically ineffective in the induction of ovulation. In contrast, women with hypogonadotropic hypogonadism respond well to gonadotropin injections or pulsatile GnRH treatment. Failure to have a withdrawal uterine bleed following the administration of progesterone is presumptive evidence of severe hypoestrogenism in women with anovulation and an anatomically normal uterus.[79] Clomiphene is unlikely to effectively induce ovulation in this setting. Maruo et al.[80] have reported that clomiphene induction of ovulation has a low chance of success in women with triiodothyronine levels below 80 ng/mL, levels sometimes seen in hypothyroidism, malnutrition, or with eating disorders. CC is also unlikely to be effective in women with a consistently elevated FSH concentration (depletion of oocyte pool). Although clomiphene is relatively contraindicated in women with pituitary tumors, it has been reported to be effective in the induction of ovulation in women with a prolactinoma who did not ovulate with bromocriptine treatment alone.[81]

The FDA-approved dosages for clomiphene are 50 or 100 mg daily for a maximum of 5 days/cycle. After spontaneous menses, or the induction of menses with a progestin withdrawal, clomiphene is started on cycle day 3, 4, or 5 at 50 mg daily for 5 days. Starting clomiphene on cycle day 3 or 5 does not appear to influence the per-cycle pregnancy rate.[82] In properly chosen women, approximately 50% will ovulate at the 50 mg daily dosage; another 25% will ovulate if the dose is increased to 100 mg daily.[83] During each cycle, determination of ovulation should be attempted. In most patients, ovulation occurs approximately 5 to 12 days after the last dose of clomiphene. Measurement of the urinary LH surge is recommended to assist the couple in prospectively determining the preovulatory interval, which is the optimal time for achieving pregnancy.

Although the FDA has approved maximal clomiphene doses of 100 mg daily, a woman who does not ovulate with a clomiphene dose of 100 mg daily for 5 days may ovulate if her dose is increased to 150 mg daily for 5 days. Of the women who do not ovulate at doses of 100 mg daily, up to 70% will ovulate at higher doses, but less than 30% become pregnant.[84]

Anovulatory women have a fecundability of 0.00 without treatment. Over the first 3 to 6 cycles of clomiphene treatment, the fecundability is in the range of 0.08 to 0.25. In cases where the only fertility factor is anovulation in the female partner, fecundability with clomiphene treatment is in the range of 0.15 to 0.25 (Fig. 22.4).[85] Clomiphene is one of the few fertility treatments that cost less than $100 and can result in a significant increase in fecundability. Clomiphene is less likely to induce ovulation in women with hyperandrogenemia, markedly elevated BMI, amenorrhea, or advanced age.[86] After 3 to 6 months of clomiphene treatment, fecundability appears to decline. Following 3 clomiphene cycles with documented ovulation and no pregnancy, experts recommend that a new approach to treatment be considered rather than continuing with clomiphene therapy.

Prior to initiating a clomiphene cycle, many experts obtain a pregnancy test to rule out an ongoing pregnancy, then prescribe a progestin withdrawal. A commonly used progestin withdrawal is medroxyprogesterone acetate (Provera) 10 mg daily for 5 days. The first day of full withdrawal flow following the cessation of the progestin treatment is day 1 of the cycle.

During the clomiphene treatment cycle, urine LH measurements can be measured by the patient at home to identify the preovulatory LH surge. The LH surge typically occurs 5 to 12 days after the last day of clomiphene medication. The woman's maximal fertile time is the day before the urine LH surge, the day of the urine LH surge, and the day following the urine LH surge. Coitus should occur on at least 2 of these 3 days. Alternatively, if the woman prefers not to measure urine LH she can have coitus with her partner every other day for 8 days beginning 5 days after the last clomiphene tablet. Evidence for successful clomiphene-induced ovulation is an appropriately drawn serum progesterone level greater than 8 ng/mL. In most clomiphene cycles resulting in successful ovulation and pregnancy, the serum progesterone level is greater than 20 ng/mL. If a menses does not occur within 17 days following the LH surge, a pregnancy test can be obtained.

Some epidemiologic studies reported that clomiphene may increase the risk of ovarian tumors, including borderline tumors and ovarian cancer. However, most recent studies

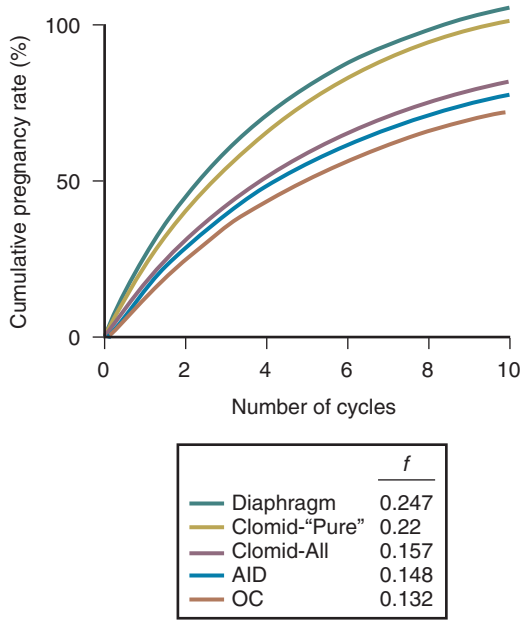

FIGURE 22.4 Cumulative pregnancy rates in women treated with clomiphene for infertility, women discontinuing contraception with the diaphragm or oral contraceptives *(OC)*, and women treated with donor insemination *(AID)*. *(From Hammond MC: Monitoring techniques for improved pregnancy rates during clomiphene ovulation induction.* Fertil Steril *42:503, 1984, with permission.)*

have not detected an increase in ovarian borderline tumors or ovarian cancer in women exposed to clomiphene.[87-90]

The role of hCG administration in enhancing the pregnancy rate associated with clomiphene treatment is controversial. Some authorities believe that the combination of clomiphene and a single dose of hCG may increase the efficacy of clomiphene induction of ovulation when women do not ovulate on standard doses of clomiphene.[91] However, in most trials, hCG administration does not consistently improve pregnancy rate compared to women who use urinary LH testing to detect the preovulatory window.[92]

In one study of 2369 clomiphene-induced pregnancies, 7% were twins, 0.5% were triplets, 0.3% were quadruplets, and 0.13% were quintuplets.[76] The most common symptoms experienced by women taking clomiphene include: vasomotor symptoms (20%), adnexal tenderness (5%), nausea (3%), headache (1%), and, rarely, blurring of vision or scotomata. Most clinicians permanently discontinue clomiphene treatment in women with clomiphene-induced visual changes.

Clomiphene Plus Glucocorticoid Induction of Ovulation

Women with PCOS who have failed to ovulate using standard doses of clomiphene are referred to as being *clomiphene resistant*. A consensus panel of expert fertility specialists recommended that for women with PCOS who are clomiphene resistant, the most appropriate next steps in treatment is gonadotropin injections or laparoscopic ovarian drilling.[93] However, for many women these options may be prohibitively expensive. For the clomiphene-resistant woman with PCOS, what treatment can be prescribed that is affordable?

Many clomiphene-resistant women will ovulate if they are treated with a combination of both clomiphene and dexamethasone. Before initiating combination therapy with clomiphene plus dexamethasone, the results of the infertility work-up should be reviewed to be sure that tubal and male factors are not contributing to the fertility problem. Two randomized, clinical trials have reported that, in clomiphene-resistant women, dexamethasone plus clomiphene treatment results in an increase in ovulation and pregnancy rates compared to clomiphene alone.[94,95] One regimen that has been reported to be successful is to treat the clomiphene-resistant woman with clomiphene 100 mg daily for cycle days 3 to 7, and *simultaneously* treat her with dexamethasone 2 mg daily for cycle days 3 to 12 (Fig. 22.5).[94] Treatment with dexamethasone reduces the serum concentration of androgens, thereby increasing the efficacy of the clomiphene. In the randomized trial that used this regimen to treat clomiphene resistant women, the ovulation rate was 75% in the clomiphene plus dexamethasone group and 15% in the clomiphene alone group ($P < .001$). The pregnancy rate was 40% in the clomiphene plus dexamethasone group and 5% in the clomiphene alone group ($P < .05$). Other investigators have also reported that a glucocorticoid is an effective adjuvant to clomiphene treatment for certain women.[96-98]

Many clinicians instruct their patients to take the dexamethasone at night to maximally blunt the early morning corticotropin adrenocorticotropic hormone (ACTH) surge, which stimulates adrenal androgen production. However, experienced clinicians have found that for many women a nighttime dose of dexamethasone energizes them and causes difficulty in falling and remaining asleep. Some experts recommend that patients take the dexamethasone in the morning. If the combination of clomiphene (100 mg daily for 5 days) plus dexamethasone does not cause ovulation, a cycle with a clomiphene dose of 150 mg daily for cycle days 3 to 7 plus dexamethasone can be prescribed. If this regimen does not cause ovulation, the patient should consider other options for ovulation induction, such as weight loss, gonadotropin injections, laparoscopic ovarian drilling, or IVF.

Clomiphene and Estrogen-Progestin Contraceptive Pretreatment

A risk factor for failure to ovulate with clomiphene is a baseline elevated circulating testosterone level. Estrogen-progestin pretreatment prior to a cycle of clomiphene may improve ovulation rates by suppressing circulating testosterone prior to the initiation of a clomiphene cycle. In one small case series and one randomized trial, 2 months of continuous estrogen-progestin contraceptive pill prior to treatment with clomiphene was reported to decrease circulating testosterone and improve ovulation and pregnancy rates in women with PCOS who had failed to ovulate with clomiphene 150 mg daily for 5 days.[99] In the randomized trial, 48 women who had failed to ovulate with clomiphene 150 mg daily for 5 days were randomized to 42 to 50 days of pretreatment with an estrogen-progestin contraceptive (ethinylestradiol 0.03 mg plus desogestrel 0.15 mg daily with no break) followed by clomiphene 100 mg daily for 5 days, or clomiphene alone.[100] The oral contraceptive regimen (OCP) significantly reduced circulating testosterone prior to the initiation of clomiphene. The ovulation rate was 65% and 11% in the OCP-CC group versus the CC group, respectively.

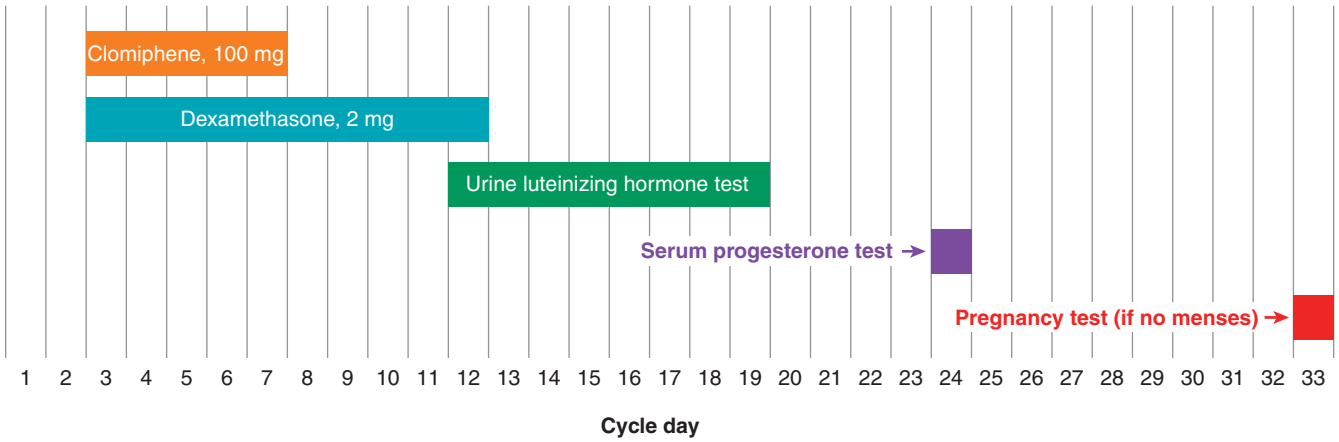

FIGURE 22.5 Schematic outline of a combined clomiphene plus dexamethasone cycle for women who are resistant to ovulation with clomiphene monotherapy.

Per-cycle pregnancy rates were 54% and 4%, respectively. A regimen of OCPs followed by clomiphene may be clinically indicated in women who have failed to ovulate with clomiphene or in women known to have an elevated total testosterone. A large-scale randomized trial of this sequential regimen is warranted.

Clomiphene and Nonclassical Adrenal Hyperplasia

Many authorities recommend that infertile anovulatory women with nonclassical adrenal hyperplasia (NCAH) due to mutations in *21-hydroxylase* receive glucocorticoids, such as prednisone 5 to 7.5 mg daily, for induction of ovulation. However, some women with long-standing NCAH also have evidence of ovarian hyperandrogenism and polycystic ovarian morphology on ultrasound. Clomiphene alone or clomiphene plus glucocorticoids can be used to induce ovulation and achieve pregnancy in infertile women with NCAH.[101,102]

Clomiphene Plus Gonadotropin Induction of Ovulation

In women who do not ovulate with standard doses of CC, gonadotropin injections can be added to clomiphene treatment to induce ovulation.[103] The main benefit of this approach to ovulation induction is that it tends to reduce the quantity of gonadotropins needed to induce ovulation during each cycle. The initial rise in LH and FSH induced by clomiphene increases the sensitivity of the follicles to respond to the gonadotropin injections. Typically, clomiphene at doses of 100 to 200 mg daily is administered for 5 days, followed by the initiation of FSH or LH-FSH injections. Investigators have reported that this regimen is associated with a 50% decrease in the dose of gonadotropin required to induce ovulation.[104,105]

Clomiphene and Metformin

Hyperinsulinemia is a common endocrine abnormality observed in women with PCOS (see Chapter 21). The elevated insulin levels contribute to reproductive dysfunction by suppressing hepatic sex-hormone-binding globulin production and possibly by acting as a co-gonadotropin with LH resulting in the stimulation of thecal cell androgen synthesis. Thus, reducing insulin levels is a therapeutic goal in women with PCOS.

Metformin is an oral biguanide antihyperglycemic agent approved for the treatment of type 2 diabetes mellitus. Metformin decreases blood glucose by inhibiting hepatic glucose production and by enhancing peripheral glucose uptake, possibly by interacting with the Peutz-Jegher syndrome tumor suppressor gene *(LKB1)*, which activates adenosine-monophosphate-activated protein kinase.[106] It increases insulin sensitivity at the postreceptor level and stimulates insulin-mediated glucose disposal. Generic extended release metformin is available in doses of 500, 750, and 1000 mg tablets. The target metformin dose is in the range of 1500 to 2550 mg daily. When using metformin extended-release tablets, the entire daily dose is given at dinner time. To minimize gastrointestinal adverse effects like nausea, many clinicians recommend that metformin should be started at 500 or 750 mg daily for 1 week, followed by an increase in the dose to the target range. If metformin is used as monotherapy, progesterone levels can be measured periodically at appropriate days to determine if ovulation has occurred, or the patient can keep a BBT record. If ovulation has not occurred after 5 to 10 weeks of metformin monotherapy, then clomiphene, 50 mg daily for 5 days, can be administered in conjunction with metformin. If the patient becomes pregnant, the metformin therapy can be discontinued. Metformin is a category B drug for pregnant women and has been used by some clinicians to treat type 2 diabetes and gestational diabetes in pregnant women.

The most common adverse effects associated with metformin are gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal bloating. In rare cases, metformin treatment has caused fatal lactic acidosis. In most of these cases, some degree of renal insufficiency was present. Although lactic acidosis caused by metformin is rare, the FDA recommends that prior to initiating treatment with metformin, the patient's serum creatinine concentration should be measured and demonstrated to be less than 1.4 mg/dL. Other insulin sensitizers may also be effective in the induction of ovulation, either alone, or in combination with clomiphene or gonadotropins.

Clinical trials have reported conflicting results concerning the relative efficacy of metformin versus clomiphene. In general, the majority of large-scale clinical trials have reported that both metformin and clomiphene monotherapy

are effective at inducing ovulation in women with PCOS, but clomiphene results in a greater per cycle ovulation, conception, and birth rates than metformin. In one study, 626 women with anovulatory infertility caused by PCOS were randomized to receive clomiphene alone, metformin alone, or clomiphene plus metformin.[107] The live birth rate was 27% in the clomiphene-metformin group, 23% in the clomiphene group, and 7% in the metformin monotherapy group. In contrast, other investigators have reported that single-agent treatment with clomiphene or metformin results in similar pregnancy rates.[108] In some studies, metformin appears to be more effective in inducing ovulation in women with an above average waist-to-hip ratio, a marker of increased visceral fat.[109] For a woman with anovulatory infertility due to PCOS who has failed to become pregnant with clomiphene, FSH treatment or ovarian drilling is more likely to result in pregnancy than treatment with clomiphene plus metformin.[110] However, if FSH treatment or ovarian drilling are not available to the patient because of their high cost, adding metformin to clomiphene or switching to letrozole ovulation induction are low-cost options.

Clomiphene versus Tamoxifen or Raloxifene for Ovulation Induction

Clomiphene, tamoxifen, and raloxifene are mixed estrogen agonists-antagonists with varying degrees of agonist or antagonist activity in different end organs. In a randomized trial, 371 with anovulatory infertile women with PCOS were randomized to receive CC 100 mg daily or tamoxifen 20 mg daily for 5 days. The ovulation rate was 64% in the clomiphene group and 52% in the tamoxifen group ($P = .01$), and the pregnancy rate was 19% and 11% in the clomiphene and tamoxifen groups, respectively ($P = .04$).[111] Clomiphene at a dose of 100 mg daily appears to be superior to tamoxifen at a dose of 20 mg daily for the induction of ovulation in women with PCOS. In a small clinical trial, 5 days of treatment with clomiphene 100 mg daily or raloxifene 100 mg daily resulted in a similar rate of ovulation, but the pregnancy rate was not studied in this trial.[112]

Gonadotropin Induction of Ovulation

◆ *The Achilles heel of gonadotropin ovulation induction is the high risk of a multiple gestation pregnancy.*

The use of gonadotropins, gonadotropins plus GnRH antagonists, and gonadotropins plus growth hormone to treat infertility; and the prevention and treatment ovarian hyperstimulation syndrome (OHSS) are discussed in detail in Chapter 30. Important concepts related to the use of gonadotropins to treat anovulatory infertility is that women with the best prognosis for success have hypogonadotropic hypogonadism (WHO I) (Fig. 22.6) and are younger than 35 years of age (Figs. 22.7 and 22.8).

Ovarian Surgery for Ovulation Induction in Polycystic Ovary Syndrome

Ovarian wedge resection was one of the first treatments used to induce ovulation in women with PCOS. However, classical ovarian wedge resection was associated with ovarian and tubal adhesions. Laparoscopic ovarian drilling using

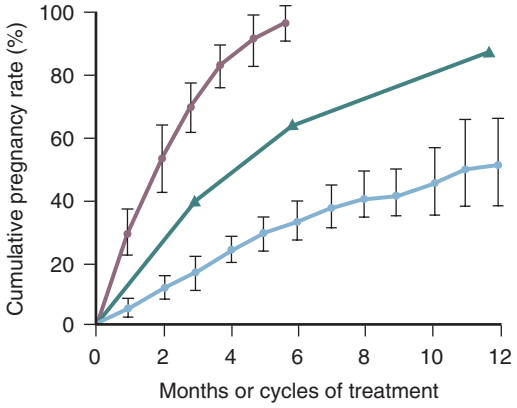

FIGURE 22.6 Cumulative pregnancy rates for infertile anovulatory women treated with gonadotropins for ovulation induction. The *pink line* represents the cumulative pregnancy rate in women in World Health Organization *(WHO)* Group I. The *blue line* represents the cumulative pregnancy rate in women in WHO Group II, who have failed induction of ovulation with clomiphene. For comparison, the *triangles* represent cumulative pregnancy rate in normal women. *(From Dor I, Itzkowic D, Mashiach S: Cumulative pregnancy rates following gonadotropin therapy.* Am J Obstet Gynecol *136:102–105, 1980, with permission.)*

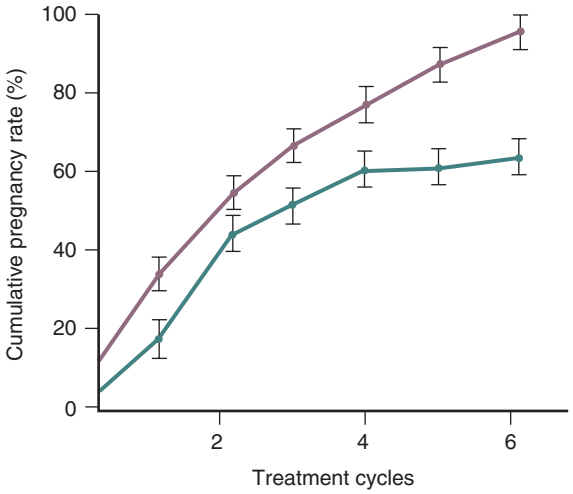

FIGURE 22.7 Cumulative pregnancy rates for hypogonadotropic anovulatory women (World Health Organization Group I) treated with gonadotropins. The *pink line* represents the cumulative pregnancy rate in women less than 35 years old. The *teal line* represents the cumulative pregnancy rate in women more than 35 years old. *(From Lunenfeld B, Insler V: Human gonadotropins. In: Wallach EE, Zacur HA, editors:* Reproductive medicine and surgery. *St. Louis, 1995, Mosby, p 617.)*

insulated needle cautery has been reported to be associated with a 70% rate of ovulation and a 50% pregnancy rate.[113] It should be noted that ovarian drilling is a second-line treatment for anovulatory infertility due to PCOS, and first-line treatments including clomiphene and letrozole should always be used before considering ovarian drilling.[114] The procedure can be performed by immobilizing the ovary with a probe and inserting an insulated needle electrode into the ovary. A cutting current of 100 watts can be used to ease the needle into the ovarian cortex. After the needle is inserted into the ovary, a 40-watt coagulating current is applied for

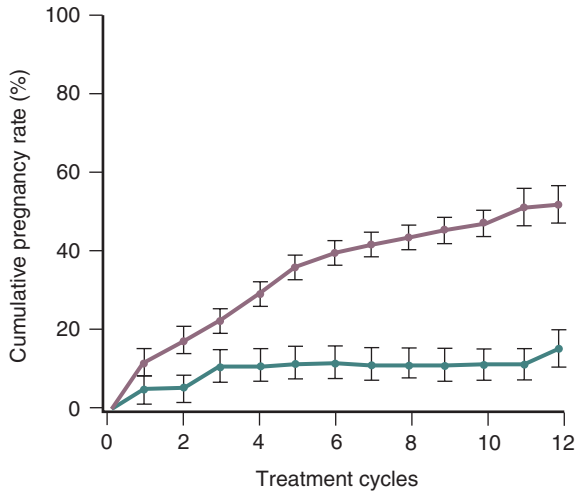

FIGURE 22.8 Cumulative pregnancy rates following gonadotropin treatment for anovulatory women who did not respond to clomiphene induction of ovulation (World Health Organization Group II). The *pink line* represents the cumulative pregnancy rate in women less than 35 years old. The *teal line* represents the cumulative pregnancy rate in women more than 35 years old. *(From Lunenfeld B, Insler V: Human gonadotropins. In: Wallach EE, Zacur HA, editors:* Reproductive medicine and surgery. *St. Louis, 1995, Mosby, p 617.)*

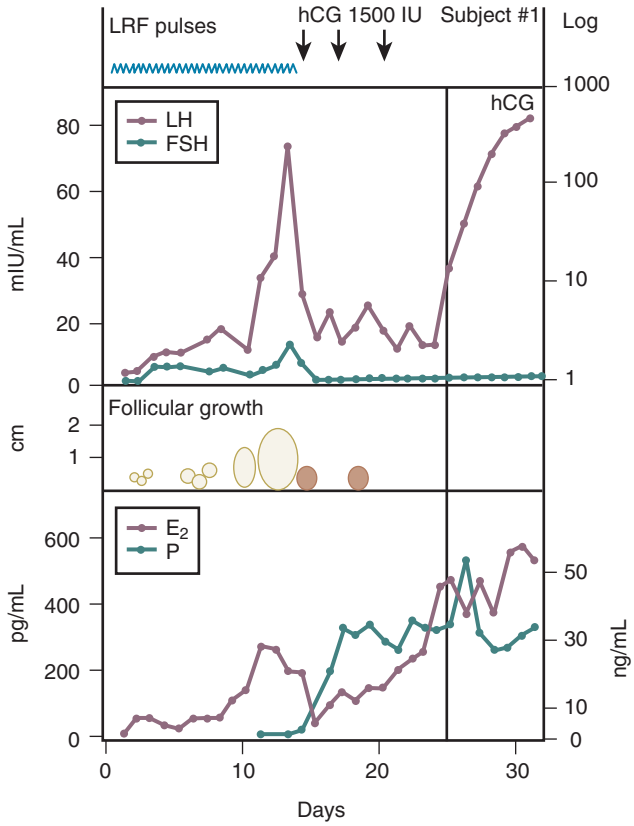

FIGURE 22.9 Endocrine and ovarian follicular response to induction of ovulation with gonadotropin-releasing hormone, 5 μg intravenous bolus over 2 hours. *E_2*, Estradiol; *FSH*, follicle stimulating hormone; *hCG*, human chorionic gonadotropin; *IU*, international units; *LH*, luteinizing hormone; *LRF*, luteinizing hormone releasing factor (more commonly known as *gonadotropin-releasing hormone*); *mIU*, milli-international units; *mL*, milliliters; *ng*, nanograms; *P*, progesterone; *pg*, pictograms. *(From Reid RL, Leopold GR, Yen SSC: Induction of ovulation and pregnancy with pulsatile luteinizing hormone releasing factor: dosage and mode of delivery.* Fertil Steril *36:565, 1981, with permission.)*

2 seconds at each point of puncture. Each ovary can be treated with 5 to 10 punctures; smaller ovaries should be treated with fewer punctures. In general, one or two punctures are not adequate to ensure ovulation postoperatively.[115] At the completion of the procedure, 1000 mL of crystalloid solution can be left in the pelvis.

In one clinical trial, 88 anovulatory, infertile women with PCOS who had not ovulated with clomiphene were randomized to ovarian surgery, FSH injections, or combination LH-FSH injections. The ovulation rate (70%) and the pregnancy rate (50%) were similar in all three groups. The spontaneous abortion rate was higher in the two groups that received gonadotropins. The investigators concluded that ovarian surgery was as efficacious as gonadotropin injections for ovulation induction in women with PCOS who did not ovulate with clomiphene.[116] In another clinical trial, women with PCOS who failed to ovulate with clomiphene 150 mg daily for 5 days were randomized to gonadotropin injections or laparoscopic ovarian diathermy. Six months after surgery, the cumulative spontaneous pregnancy rate was 28%. After 3 cycles of gonadotropin injections, the cumulative pregnancy rate was 33%.[117]

The risks of ovarian surgery for women with hirsutism are greater than the potential benefits. However, for women with PCOS and infertility who have been unable to become pregnant with weight loss, clomiphene and metformin treatment, the option of ovarian surgery for ovulation induction may be warranted prior to induction of ovulation with FSH. Survey data indicate that many patients prefer one surgical intervention compared to ovulation with FSH injections, if the two treatments have comparable success rates.[118]

Cost-benefit analyses suggest that laparoscopic surgery for ovulation induction is associated with less healthcare costs than FSH injections.[119] Other authorities believe that the rare serious risks associated with surgery makes FSH injections the preferable option.[120]

Pulsatile Administration of Gonadotropin-Releasing Hormone

◆ *Pulsatile administration of GnRH is not available in the United States but is available in many European countries.*

A key feature of hypothalamic biology is the pulsatile release of the decapeptide GnRH from the arcuate nucleus into the pituitary portal circulation. The pulsatile release of GnRH stimulates the pituitary to produce LH and FSH in a pulsatile manner. In turn, pituitary gonadotropin secretion stimulates follicular development, ovulation, and progesterone secretion in the luteal phase. In women with hypogonadotropic hypogonadism and anovulation (low levels of endogenous gonadotropins and decreased endogenous estrogen production), the pulsatile administration of GnRH is effective in inducing ovulation (Fig. 22.9). The advantages of GnRH induction of ovulation include a reduced need for cycle monitoring and a reduced risk of multiple gestation due in

part to an intact pituitary feedback system. The main disadvantage of pulsatile GnRH therapy is that the infusion pump and subcutaneous delivery system may be difficult for patients to maintain. Pulsatile GnRH for ovulation induction is currently not available in the United States.

Santoro et al.[121] proposed eight criteria for identifying women most likely to safely achieve ovulation with pulsatile GnRH:

1. Primary or secondary amenorrhea for at least 6 months
2. Absence of hirsutism, galactorrhea, or ovarian enlargement
3. Weight not below 90% of ideal body weight
4. No excessive exercise or stress
5. Normal serum prolactin, TSH, dehydroepiandrosterone sulfate (DHEAS), and testosterone concentrations
6. Low gonadotropin concentrations
7. No evidence of a structural central nervous system lesion
8. No recent hormone treatment

GnRH is administered using a computer-driven pump that delivers one pulse of GnRH every 90 minutes at a dose of 75 to 100 ng/kg per pulse. In Europe, doses of 10 to 30 μg per pulse are commonly used. Interpulse intervals as short as 1 hour[121] or as long as 2 hours[122] have been successfully used. GnRH doses as low as 25 ng/kg per pulse can successfully induce ovulation, but are associated with subnormal luteal phase progesterone secretion.[121] Both intravenous and subcutaneous administration of GnRH have been successfully used to induce ovulation. Intravenous administration probably results in a more reliable induction of ovulation, but this route is associated with more technical problems (restarting the intravenous catheter) and risk of infection than subcutaneous administration. The intensity of clinical monitoring can range from regular follicle monitoring with sonography and serum estradiol measurements to BBT measurement with use of an ovulation predictor kit. Low-intensity monitoring is acceptable because the risk of multiple pregnancy or ovarian hyperstimulation is low with pulsatile GnRH therapy.

Studies that compare the efficacy of gonadotropin versus pulsatile GnRH induction of ovulation report that pulsatile GnRH induction of ovulation may be associated with superior ovulation and pregnancy rates than gonadotropin treatment.[123,124] The risk of multiple gestation is higher with gonadotropin treatment (14%) than with pulsatile GnRH treatment (8%).[125] This increased risk is due to a higher rate of multifollicular development with gonadotropin treatment (48% of cycles) than with pulsatile GnRH treatment (19% of cycles). Pulsatile GnRH results in a decreased risk of high-order multiple gestation when compared with gonadotropin treatment.[126]

Hyperprolactinemia

Infertile women with hyperprolactinemia and anovulation often achieve pregnancy after treatment with a dopamine agonist, such as bromocriptine or cabergoline. The treatment of hyperprolactinemia is discussed in Chapter 3.

Luteal Phase Deficiency

Luteal phase deficiency has been defined as a condition in which the ovarian secretion of progesterone is not sufficient to maintain a functional secretory endometrium that supports embryo implantation and growth. The gold standard test for identifying luteal phase deficiency is histologic dating of tissue from an endometrial biopsy that demonstrates a developmental lag of at least 2 days. However, most recent research indicates that delayed maturation of the endometrium is observed at a similar rate in both fertile and infertile women.[127] Most authorities believe that luteal phase deficiency is not a major independent cause of infertility.[128]

From an endocrine perspective, follicular or luteal function that is far outside the normative range is likely associated with reduced fertility. In the most extreme example, it is known that resection of the corpus luteum and the associated reduction in progesterone secretion reduces fertility and causes abortion in women prior to about 49 days of pregnancy.[129] In addition, numerous clinical trials have observed that luteal phase progesterone support improves pregnancy rates following IVF cycles involving controlled ovarian hyperstimulation and ovarian follicle puncture to harvest oocytes.[130] It is probable that an occasional case of infertility may be caused by poor follicle development and inadequate corpus luteal secretion of progesterone or a relative resistance to progesterone effect in the endometrium. However, it is unlikely that luteal phase deficiency is a common cause of infertility.

Aging Ovary, Aging Follicle

◆ *Current approaches to fertility treatment cannot reverse the detrimental effect of ovarian aging on fecundability.*

An immutable feature of ovarian physiology is that the number of oocytes and follicles are fixed in utero and decline following an exponential curve (mathematically similar to the curve for the decay of radioactive material) from the second trimester, as shown in Fig. 22.10 (see also Chapters 8 and 14). At birth, an estimate of the number of oocytes and follicles in a pair of human ovaries is approximately 2 million. At the completion of puberty, the number of oocytes in a pair of human ovaries is in the range of 250,000. After 35 to 37 years of age, the rate of loss of oocytes and follicles appears to accelerate.[131,132] During adult reproductive life, follicles most sensitive to the growth-promoting effects of FSH are first selected to become the dominant follicle. As the ovary and the residual follicular pool age, the remaining follicles appear to be relatively resistant to FSH. The aging follicle contains an oocyte that is less likely to result in a successful pregnancy. The decrease in fecundability associated with aging is probably due to a decline in both the quantity and quality of follicles and oocytes.[133] The decrease in quality is likely associated with dysfunction in intracellular mechanisms necessary for oocyte meiosis, fertilization, and embryo growth. Data to support the concept that the aging oocyte is less likely to result in a successful pregnancy come from multiple sources (see Figs. 22.7 and 22.8).

Most mammalian species do not have histologically detectable mitotic oogonia or germ stem cells in the adult ovary. However, recent studies in rodents and humans have reported that there are stem cells in the adult ovary that can be harvested, stimulated to undergo mitotic replication, and then be triggered to form competent oocytes.[134] The generation of functional oocytes from primordial germ cells has

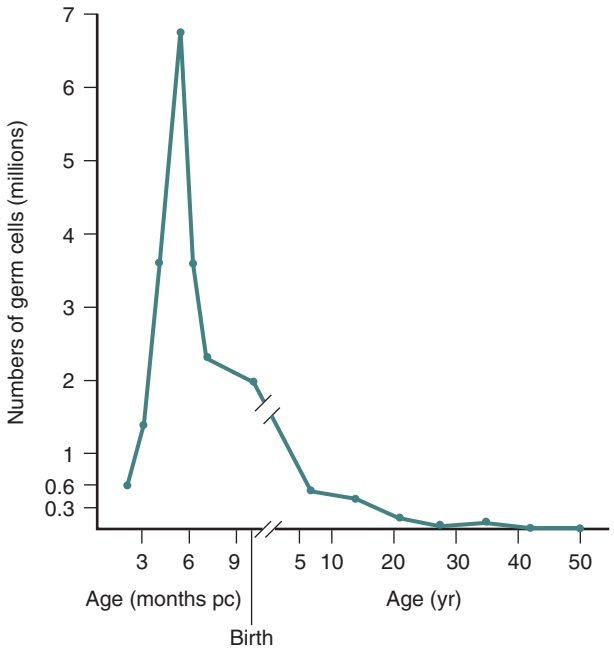

FIGURE 22.10 Changes in the total number of oocytes (and follicles) in human ovaries before and after birth. The number of germ cells in the ovary peaks in utero during the second trimester. *(From Baker TC: Radiosensitivity of mammalian oocytes with particular reference to the human female.* Am J Obstet Gynecol *110:746–761, 1971.)*

been best documented in the mouse model. In the mouse, using primordial germ cells, functional oocytes have been generated in vitro, and a live birth has occurred following fertilization and intrauterine transfer of the fertilized oocyte. Mitochondrial dysfunction has been hypothesized to be a major cause of age-related decline in oocyte function. In an attempt to rejuvenate oocytes in older women, investigators have explored the role of autologous mitochondrial injection (AMI). In this process, the ovarian cortex is harvested with laparoscopic surgery and purified oogonial precursor cells (OPCs) are prepared from the tissue. Mitochondria are isolated from the OPCs and injected into aging oocytes during an IVF cycle using intracytoplasmic sperm injection. The AMI procedure has been reported to be associated with good oocyte fertilization rates (78%) and some pregnancies.[135] A large randomized trial would be needed to definitively test the effectiveness of this innovative treatment and assess its impact on newborn outcomes, including congenital malformations.

Mathematical descriptions of the decline in ovarian follicles and oocytes favor one of three models: (1) an exponential rate of decline with a fixed "half-life," similar to models describing the decay of radioactive material; (2) an exponential rate of decline with two distinct rates of decline, a slow rate of decline early in life, and a more rapid rate of decline later in reproductive life; and (3) a power model where the rate of decline accelerates throughout a woman's life.[136] The rate of decline of AMH, a biochemical marker of ovarian follicle number, and the AFC assessed by sonography also appear to accelerate with female aging, supporting the power model of decline.[137]

The discovery of interventions that could prevent the decline of oocytes and follicles in the adult ovary is an important priority. In the mouse model, caloric restriction or knockout of the peroxisome proliferator-activated receptor γ coactivator-1α, a component of a metabolic regulatory pathway, were reported to delay the rate of oocyte loss.[138]

For infertile couples where the cause of the infertility is azoospermia in the male partner, the success of donor sperm insemination is directly related to the age of the female partner. In a study of 1654 women undergoing donor insemination, the cumulative live birth rate after 12 cycles decreased from 87% for women 20 to 29 years of age to 66% and 52% for women 38 to 39 years and 40 to 45 years of age, respectively.[139] Data from IVF programs demonstrate that the age of the female partner is an important determinant of pregnancy rates. In 2014 for women younger than 35 years of age, the live birth rate per cycle was 49% compared to 20% in women 38 to 40 years of age, and 11% in women 41 to 42 years of age.[140] The poor functional quality of oocytes in the terminal follicle pool is a major cause of the relationship between female aging and diminishing fecundability. The poor functional quality of these oocytes is supported by the observed high rate of aneuploid blastocytes and trisomic pregnancy that occurs following their fertilization,[141,142] and the poor performance of these oocytes in the process of IVF, including poor fertilization, embryonic growth, low implantation, and pregnancy rates.

Four major measurements are used to assess the size of the ovarian follicle and oocyte pool in infertile women: (1) AMH concentration measured at any time in the menstrual cycle; (2) menstrual cycle day 3 FSH and estradiol concentration; (3) AFC by transvaginal sonography; and (4) the CCCT.[143,144] Measurement of cycle day 3 inhibin B concentration can also be used to assess the size of the ovarian follicle and oocyte pool, but this test is seldom used in clinical practice because of technical difficulties in the measurement of this analyte. In the normal menstrual cycle, decreases in estradiol and inhibin A during menses are associated with an increase in FSH production during the first 5 days of the menstrual cycle (see Chapters 7 and 8). The magnitude of the rise in FSH during menses is dependent on the magnitude of negative feedback provided by the circulating inhibin B concentration, a constitutively secreted hormone from small follicles. The greater the number of small follicles, the greater the inhibin B concentration during menses, the greater the inhibin B negative feedback on FSH, and the smaller the rise in FSH during menses. The increase in FSH during menses stimulates the growth of an ovarian follicle that will be selected to achieve dominance during the cycle. As the selected follicle grows, it secretes increasing quantities of estradiol, inhibin B, and inhibin A, thereby suppressing FSH production to low levels. As the follicular pool declines, inhibin B levels during menses decline and the magnitude of the FSH increase during menses increases, resulting in elevated serum FSH concentrations on cycle days 2, 3, and 4. A cycle day 3 FSH greater than 10 mIU/mL is associated with reduced fecundability, which is likely due to an aging ovarian follicle pool. Some women with diminished ovarian reserve are noted to have estradiol greater than 80 pg/mL on cycle day 3. This finding suggests that there was an increase in FSH late in the luteal phase, accelerating follicle growth during menses. Consequently, an estradiol greater than 80 pg/

mL is a sign of diminished ovarian reserve.[145,146] AMH is expressed by granulosa cells from small follicles, so as the follicle pool declines, serum AMH decreases.[147,148] AMH levels are relatively constant throughout the menstrual cycle, increasing the convenience of obtaining a clinically useful AMH measurement compared with the timed measurements required for the interpretation of FSH values. An elevated serum FSH on cycle day 3 or a decreased cycle day 3 inhibin B or a decreased AMH at any time during the cycle are good biochemical markers of a depleted follicular pool. A depleted follicle and oocyte pool is associated with decreased fecundability, an increased rate of pregnancy loss, and an increased rate of aneuploid pregnancy. Particularly in infertile women older than 35 years of age, measurement of AMH, cycle day 3 FSH, CCCT, or AFC are very helpful in identifying women with a reduced follicular pool. In young healthy women without infertility, testing for diminished ovarian reserve is generally NOT useful in predicting time to pregnancy or fecundability.[149,150]

AFC is the sum of the number of antral follicles 2 to 10 mm in diameter in each ovary assessed in the two-dimensional ovarian slice with the greatest area by high-resolution transvaginal sonography. AFC is commonly assessed during the early follicular phase of the menstrual cycles, but some authorities report it can be performed at any time in the menstrual cycle.[151] An AFC of 4 or less is associated with a poor follicular response to ovarian hyperstimulation, resulting in the development of a low number of large antral follicles, and in IVF cycles, the retrieval of a low number of oocytes. An AFC of 10 or less is also associated with reduced ovarian response compared to an AFC greater than 10.[152,153] The AFC has good interobserver reliability, and the AFC shows much more variation between women than within the same woman measured in multiple tests.[154]

During menses, negative feedback control of FSH is largely from inhibin B, and to a lesser degree from estradiol. Following the administration of an estrogen antagonist such as clomiphene, the estradiol negative feedback is blocked and FSH negative feedback is only from inhibin B, resulting in a greater rise in FSH. This may increase the sensitivity of the measurement of FSH to detect a depleted follicle pool. The CCCT is performed by administering clomiphene, 100 mg daily for 5 days from cycle day 5 to 9. FSH levels are drawn on cycle days 3 and 10. An elevated FSH level on either cycle day 3 or 10 is associated with a diminished ovarian follicular pool and reduced fecundability. In some series, for every 100 women with an elevated day 10 FSH (postclomiphene challenge), only 40 have an elevated day 3 FSH (preclomiphene challenge). Women who may be candidates for the CCCT include those over 35 years of age, cigarette smokers, and women with unexplained infertility, stage III or IV endometriosis, previous bilateral ovarian surgery, or history of poor response to FSH stimulation. Investigators have reported that the measurement of FSH after a course of CC is more sensitive for identifying women with diminished ovarian reserve than is the cycle day 3 FSH test.[155,156] Other investigators have reported that basal FSH and the clomiphene challenge test have similar performance in identifying women with decreased fecundity due to a depleted follicle pool.[157]

Biological markers of diminished ovarian reserve may be discordant. For example, among 5354 women 20 to 45 years of age being treated at fertility centers, 20% had AMH and day 3 FSH measurements that were discordant. Of women with reassuring day 3 FSH measurements (FSH <10 mIU/mL), AMH was low (<0.8 ng/mL) in 9% of women less than 35 years of age and 33% of women more than 40 years of age.[158] More data are needed to fully understand the clinical implications of discordant biological markers of diminished ovarian reserve.

Dozens of studies in IVF have reported that the number of mature follicles stimulated and the number of oocytes retrieved is related to basal FSH, inhibin B, AMH, and AFC.[159-161] In a classic study of the relationship between cycle day 3 FSH and pregnancy rate in an IVF program, women with a day 3 FSH concentration of less than 10 mIU/mL had an ongoing pregnancy rate of 0.18. In contrast, women with a cycle day 3 FSH level greater than 25 mIU/mL had an ongoing pregnancy rate of 0.00.[162] The cycle day 3 FSH predicts the magnitude of the ovarian response to exogenous gonadotropin stimulation—including the peak estradiol concentration, the number of follicles, and the number of oocytes that are obtained at follicular aspiration. Since measures of the size of the ovarian follicular pool predict the magnitude of the ovarian response to stimulation, these measures can be used to guide the choice of stimulation regimens. For example, using a basal AMH test to guide selection of stimulation regimens, women with low AMH levels (reduced follicle pool) would be stimulated with higher doses of gonadotropins, and women with higher levels of AMH (large follicle pool) would be stimulated with lower doses of gonadotropins.[163] Measures of the size of the follicle pool, such as AMH, can also be used to assess the magnitude of the decrease in the ovarian follicle pool following ovarian cystectomy for diseases, such as endometriosis,[164,165] or chemotherapy.[166]

Many lifestyle factors and genetic factors determine the rate of follicular loss and the age at which serum FSH measured during menses begins to rise. For example, cigarette smoking appears to hasten the pace at which the follicular pool is depleted. Menopause occurs significantly earlier in women who smoke.[167] In women in their mid-30s, cycle day 3 FSH also appears to be approximately 25% higher in cigarette smokers than in non-smokers.[168] In cigarette smokers, the number of oocytes per pair of ovaries appears to be reduced.[169]

Pelvic radiation and chemotherapy with alkylating agents are two important exposures that are associated with a diminished follicular pool. Women who are older than 30 years of age and have completed six courses of chemotherapy for Hodgkin disease typically lose more than 90% of their follicles and many enter menopause immediately after the chemotherapy.[170] Radiation doses as low as 400 rad to the ovary will induce menopause in women over 35 years of age. Girls are much more resistant to the induction of menopause with chemotherapy or pelvic radiation, probably due to their large follicular pool.

Cancer Treatment and Infertility

Issues related to fertility preservation and the treatment of infertility in cancer patients, including oocyte and ovarian cortex cryopreservation, is discussed in Chapter 33, Fertility Preservation.

Anatomical Factors in the Female

Fallopian Tube Causes of Female Infertility

◆ *Fallopian tube disease is a major cause of female infertility. Prevention of chlamydia infection will reduce the prevalence of distal occlusion of the fallopian tube.*

Successful pregnancy requires the close proximity of sperm and oocyte and the transport of an embryo into the uterine cavity. Abnormalities of the fallopian tube, uterus, cervix, or vagina can adversely impact female fertility by blocking the union of sperm and oocyte and/or preventing the transport of the embryo into the uterus. Tubal or peritoneal disease is identified in approximately 20% of the female partners of infertile couples. With the rise of assisted reproductive technology (ART) to treat tubal causes of female infertility there are limited, but important, clinical circumstances where the surgical treatment of fallopian tube problems may be indicated: (1) bilateral distal tubal blockage, (2) proximal tubal blockage, (3) identification of hydrosalpinges prior to a cycle of IVF, and (4) assessment of tubal status prior to microsurgical reanastomosis for tubal ligation reversal.[171,172] The causes of tubal disease, diagnosis, and treatment are reviewed in subsequent text.

Pelvic inflammatory disease (PID), infection with *Chlamydia trachomatis*, appendicitis, septic abortion, and previous pelvic or tubal surgery are major contributors to tubal disease. Endometriosis commonly causes peritoneal and ovarian adhesions and distorts tubal anatomy, but in almost all women with endometriosis the fallopian tubes are patent. The rate of tubal infertility has been reported to be 12%, 23%, and 54% after one, two, and three episodes of PID, respectively.[173] Subclinical pelvic infections with *Chlamydia trachomatis* is a major cause of tubal disease associated with infertility. Patton et al.[174] studied tubal biopsy specimens from 25 women with PID and tubal infertility. *Chlamydia trachomatis* was detected in 3 out of 25 specimens by culture, 12 out of 24 specimens by in situ hybridization, 15 out of 22 specimens by immunoperoxidase staining, and 2 out of 10 specimens by transmission electron microscopy. Serum antibodies against chlamydia were detected in 15 out of 21 subjects. In this cohort, chlamydia was identified in 19 out of 24 women with PID and infertility.[174] Many subsequent studies have demonstrated that circulating high-titer chlamydia antibodies are associated with tubal disease as detected at the time of laparoscopy.[175] In one large population study, the presence of chlamydia antibodies was strongly associated with tubal factor infertility.[176] Approximately 1% to 4% of women of 18 to 26 years of age are infected with chlamydia.[177] Although chlamydia is the most common cause of tubal damage in North America and Europe, tuberculosis is a common cause of distal tubal occlusion for women from Northern India and Nepal.[178] In areas with a high prevalence of tuberculosis, evaluation of the female partner for tuberculosis using a polymerase chain reaction test on an endometrial biopsy specimen identified women who would benefit from antimicrobial therapy.[179] A history of a ruptured appendix increases the risk of developing tubal factor infertility. In one case-control study, a history of ruptured appendix was associated with a 4.8-fold increase in the risk of tubal infertility. Appendicitis without rupture was not associated with an increased risk of tubal infertility.[180]

As noted above, the three most commonly used tests of tubal patency are the HSG, HyCoSy, and laparoscopy. The American College of Radiologists recommends HSG for the diagnosis of tubal disease.[181] The advantages of HSG are that it uses few resources, produces data concerning the shape of the uterine cavity, and may increase fecundability by altering the peritoneal environment. The major disadvantages of HSG are that it requires a fluoroscopy imaging device, causes pain during the performance of the procedure, and provides no information concerning the presence of peritoneal diseases, such as endometriosis and ovarian adhesions. In addition, if the HSG demonstrates proximal tubal occlusion, a confirmatory test (selective tubal catheterization or laparoscopy) is required. This additional testing is necessary because about 15% of the cases where HSG demonstrates proximal tubal occlusion are actually due to "tubal spasm" that is physiological and not a permanent anatomical state. HSG is usually performed between cycle days 5 and 12. Many centers prepare women for the procedure with an antiprostaglandin agent, like ibuprofen, immediately before the procedure. The risk of infection following HSG is in the range of 1%.[182] If the HSG demonstrates hydrosalpinges, the patient should be treated with a course of doxycycline.

Many studies report that following an HSG, fecundity is increased in the 12 to 24 months following the procedure. For example, in one clinical trial, women with infertility were randomized to HSG with an oil-based contrast media or with no intervention. After 24 months, pregnancy rates were 58% and 41% in the HSG and no intervention groups, respectively ($P = .03$).[183] The fecundability following HSG appears to be similar with oil-based and water-soluble contrast agents. In one trial, 175 women were randomized to undergo HSG with either oil-based or water-soluble contrast agents. The oil-based contrast agent gave better resolution of the uterine cavity and the aqueous agent gave better resolution of the tubal mucosa. The postprocedure pregnancy rates were similar in the two groups.[184] The main diagnostic advantage of laparoscopy over HSG is that it has better sensitivity and specificity for diagnosing ovarian and peritoneal disease than HSG. In addition, laparoscopy can diagnose endometriosis and can be used to treat abnormalities observed at the time of the procedure.

HyCoSy is performed by cannulating the cervical os and, under ultrasound imaging, injecting an ultrasound contrast media or a crystalloid into the uterus.[185] Specialized ultrasound devices that use contrast-tuned imaging are available to enhance the interpretation of the findings, but standard ultrasound devices can be used for the procedure.[186] Ultrasound contrast media are microbubbles suspended in a solution. The shell of the microbubble is made of albumin, galactose, lipids, or polymers. The bubble contains a gas that has low solubility in aqueous fluids, such as sulfur hexafluoride or octafluoropropane. The gas in the bubble generates a strong unique signature during ultrasound imaging. The media fills the uterine cavity providing an image of the shape of the cavity and can identify small intracavity filling defects caused by polyps or submucus myomas. If the proximal and distal fallopian tubes are patent, the contrast media flows

into the proximal tube and out of the distal tube into the peritoneal cavity. An alternative to an ultrasound contrast media is to use a crystalloid, such as saline, which is vigorously shaken to induce the formation of multiple air bubbles in the saline. HyCoSy is an office-based procedure that is performed in the early follicular phase. HyCoSy is associated with less pain than HSG.[187] HyCoSy has sensitivity to detect tubal disease similar to HSG, but is superior to HSG for the detection of small intracavitary lesions.[19]

As noted above, chlamydia infection is a common cause of tubal damage. One novel strategy for triaging infertile women into groups at high and low risk for tubal occlusion is the measurement of circulating anti-chlamydia antibodies. For infertile women with absent or low-titer antibodies to chlamydia, the rate of tubal damage on laparoscopy or HSG is about 5%. For infertile women with high-titer antibodies to chlamydia, the rate of tubal damage on laparoscopy or HSG is about 35%.[188] In women with high-titer antibodies to chlamydia, more severe tubal damage is observed than in women with low titer or absent antibodies.[189] Of great interest, women with patent fallopian tubes who are seropositive for chlamydia antibodies have reduced fecundability compared to women seronegative for chlamydia antibodies.[190] Until testing for anti-chlamydia antibodies as a screening strategy to identify infertile women with tubal disease is better standardized, HSG or HyCoSy remain the first-line test to evaluate tubal patency.[191]

Surgery for the treatment of infertility due to tubal disease is most successful if the disease is localized to the distal portion of the tube. *Fimbrioplasty* is the lysis of fimbrial adhesions or dilatation of fimbrial strictures. *Neosalpingostomy* is the creation of a new tubal opening in a fallopian tube with a distal occlusion. Dlugi et al.[192] evaluated the success of unilateral versus bilateral fimbrioplasty or neosalpingostomy in 113 women with tubal factor infertility. Overall, these procedures were associated with a postsurgery monthly pregnancy rate of 0.026. Similar monthly pregnancy rates following fimbrioplasty or neosalpingostomy have been reported by Canis et al.[193] In a study of 434 consecutive cases of laparoscopic surgery to treat distal tubal disease, the cumulative pregnancy rate 2 years following surgery was 28%. This translates into a monthly pregnancy rate of less than 0.015, which is greater than 0.00, but much lower than the 0.30 pregnancy rate expected after one cycle of IVF.[194] In this study, factors that reduced the success of surgical treatment included repeated surgery, previous ectopic pregnancy, the presence of severe pelvic adhesions, and positive chlamydia serology. Following tubal surgery, couples can attempt to achieve conception naturally over many menstrual cycles. When viewed from a cumulative perspective, approximately 50% of the good-prognosis patients treated with distal tubal surgery became pregnant, and approximately 10% of the pregnancies achieved were ectopic pregnancies.

Clinical factors that are associated with successful surgical treatment of distal tubal disease include tubal diameter less than 30 mm, visible fimbriae, absence of dense pelvic adhesions, absence of ovarian adhesions, female partner less than 35 years of age and good ovarian reserve (Fig. 22.11).[195] Infertile women with bilateral proximal and distal tubal disease have very low chances of conceiving following surgical treatment.[196] Treatment with IVF is much more successful than surgical treatment in this group of women.

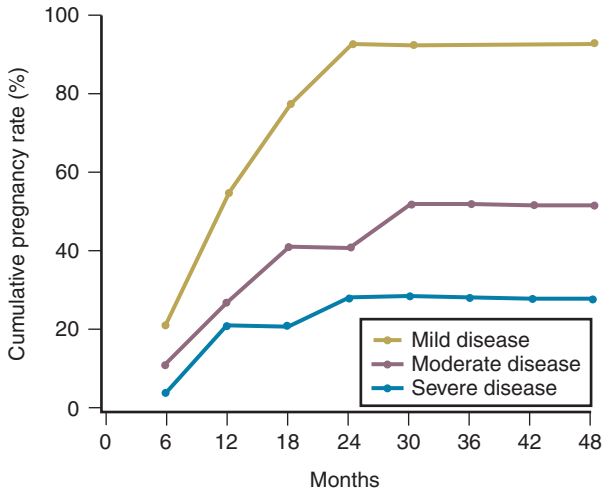

FIGURE 22.11 Life table analysis of pregnancy outcome following neosalpingoneostomy, by extent of disease. *(From Schlaff WE, Dassiakos D, Damewood MD, Rock JA: Neosalpingostomy for distal tubal obstruction: prognostic factors and impact of surgical technique.* Fertil Steril *54:984, 1990, with permission.)*

In women with tubal infertility, proximal tubal occlusion accounts for about 20% of cases. Causes of proximal tubal occlusion include mucus debris, spasm at the uterotubal junction, or occlusion. Occlusion is commonly caused by fibrosis associated with salpingitis isthmica nodosa, PID, adenomyosis, or fibroids. A major advance in the treatment of proximal tubal occlusion associated with infertility is the development of flexible tip guidewire techniques to restore patency to the proximal portion of the fallopian tube.[197] In one study of transcervical fluoroscopic catheter recanalization of proximal tubal occlusion, successful recanalization was achieved in 47 of 65 tubes treated (72%). Of the 41 women with open tubes following the procedure, 9 achieved live births (22%), 4 had ectopic pregnancies (10%), and 1 woman became pregnant but had a miscarriage. In the 11 women in whom tubal recanalization was not successful, there were no pregnancies.[198] In a large meta-analysis, tubal cannulation was successful in 85% of cases and 50% of the successfully treated women conceived.[199] If tubal cannulation cannot be accomplished, IVF is a better treatment option than surgical reimplantation of the tubes into the uterus.[200]

One of the most successful surgical procedures for infertility is the microsurgical reanastomosis of fallopian tubes that were subjected to surgical sterilization procedures. The clinical characteristics that are associated with a high success rate for surgical reanastomosis include: (1) patient under 40 years of age; (2) tubal length greater than 4 cm; (3) sterilization performed with the Falope ring, clip, or Pomeroy tubal ligation technique; and (4) absence of associated pelvic pathology. Cumulative pregnancy rates in the year following the procedure are in the range of 50% to 80%. In one large case series that studied the impact of the age of the female partner on the postreanastomosis pregnancy rate, the reported cumulative intrauterine pregnancy rates were 81%, 67%, 50%, and 13% for female partners younger than 36, 36 to 40, 40 to 43, and older than 43 years of age, respectively.[201] In another series of 1898 women undergoing tubal ligation reversal, the 5-year live birth rates were 50%, 56%, 51%,

and 26% for women 20 to 29, 30 to 34, 35 to 39, and 40 to 44 years, respectively.[202] Laparoscopic and robot assisted laparoscopic surgical reanastomosis have replaced traditional laparotomy approaches to tubal reanastomosis.[203-205] In a cohort study of the role of IVF or surgical reanastomosis for the treatment of women with a tubal sterilization who wanted to conceive, for women younger than 41 years of age, surgical reanastomosis and IVF resulted in similar cumulative pregnancy rates, but surgical reanastomosis was reported to be more cost effective than IVF.[206] An important point is that following tubal reanastomosis, the monthly pregnancy rate is in the range of 0.02 (2%), but one cycle of IVF is associated with a pregnancy rate of 0.30 (30%). Hence, if timeliness of pregnancy is important, IVF is superior to surgical reanastomosis.

For infertile women with tubal disease, treatment with IVF is associated with a pregnancy rate of approximately 30% in the first cycle of treatment. Several studies indicate that hydrosalpinges decrease the pregnancy rate in IVF cycles.[207,208] The fluid in the hydrosalpinx may contain toxic factors that decrease the implantation rate of embryos or have direct embryotoxicity.[209] A meta-analysis of three controlled trials reported that laparoscopic salpingectomy for hydrosalpinx prior to IVF increased pregnancy rates by 75% compared with not performing the surgery.[210] In one trial, 204 women were randomized to undergo salpingectomy prior to IVF or to undergo IVF without prior salpingectomy.[211] The live birth rate was 29% in the women who had salpingectomy followed by IVF and 16% in the women who had IVF alone ($P < .05$). Laparoscopic salpingectomy should be considered for all women with hydrosalpinges prior to undergoing IVF. Interestingly, in infertile women with one patent tube of normal caliber, and one blocked tube with a hydrosalpinx, surgical removal of the single blocked tube is associated with a good spontaneous pregnancy rate.[212] An alternative to salpingectomy of hydrosalpinges prior to IVF is to clip the proximal end of the tube to prevent the fluid from the hydrosalpinx to drain into the uterine cavity and disrupt embryo-endometrial interaction.[213,214] Some clinicians advise that if the proximal tube is clipped that the distal end of the hydrosalpinges should be widely fenestrated to prevent fluid from becoming trapped within the tube.

Pelvic Adhesions

Following pelvic surgery, adhesions develop in approximately 75% of women.[215] The mechanism of postoperative adhesion formation is not fully understood, but it involves invasion of fibroblasts into the postsurgical fibrinous bridges. As a result, adhesive tissue develops, connecting two normally unconnected structures or covering the surface of a structure with de novo adhesions (Fig. 22.12). In the normal peritoneal healing process, a serosanginous proteinaceous fluid exudes from the site of injury and coagulates into fibrin bands. In the normal healing process, endogenous fibrinolytic activity lyses these fibrin bands within 4 days. If the fibrinous bands are invaded by fibroblasts, angiogenesis occurs and a permanent bridge of tissue (an adhesion) is created. Factors that decrease fibrinolytic activity (ischemia, infection, drying of peritoneal surfaces) or increase fibroblast infiltration of the fibrin clot will increase the chance of developing adhesions.[216] Factors that increase fibrinolytic activity, such as plasmin

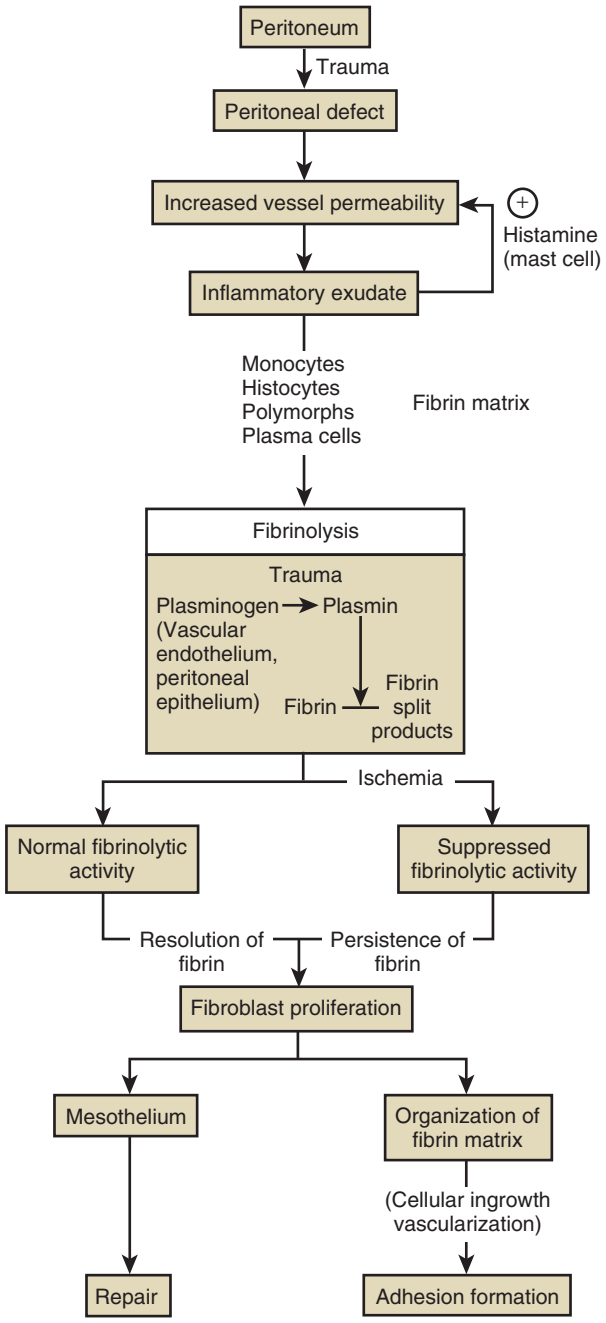

FIGURE 22.12 Schematic of the normal healing response to a surgical injury in the pelvic peritoneum. *(From Montz FJ, Shimanuki J, DiZerega CS: Postsurgical mesothelial re-epitheliazation. In: DeCherney AH, Polan ML, editors:* Reproductive surgery. *Chicago, 1987, Mosby Year Book.)*

preparations (plasmin and fibrinolysin) or plasmin activators (streptokinase, urokinase, and tissue-type plasminogen activator), are efficacious in preventing postsurgical adhesion formation.[217] Methods reported to minimize postoperative adhesions include the use of dextran, adhesion-prevention barriers like regenerated oxidized cellulose (Interceed) and expanded polytetrafluoroethylene (PTFE, Gore-Tex), heparin, glucocorticoids, fibrinolytic agents, hyaluronic acid-based fluid agents, polyethylene glycol hydrogel, and nonsteroidal antiinflammatory agents. Most of these agents have been

demonstrated to be effective in laboratory models of adhesion formation.[218-220] In humans oxidized regenerated cellulose (Interceed), expanded PTFE (Gore-Tex), and sodium hyaluronate with carboxymethylcellulose (Seprafilm) may all be more effective than no treatment in reducing adhesion formation following pelvic surgery.[221]

Oxidized regenerated cellulose (Interceed), one of the most widely studied adhesion-prevention adjuvant agents, becomes a gel shortly after placement on a surgically traumatized peritoneal surface. The gel reduces the chance of formation of fibrin bridges between two opposing structures and thereby reduces the chance of adhesion formation. The material is resorbed within 1 week as it is metabolized into glucose and glucuronic acid. Oxidized regenerated cellulose has been demonstrated to reduce adhesion formation in women in well-controlled randomized prospective studies. In one study of 66 women with bilateral adnexal adhesive disease, the use of Interceed on one adnexa resulted in a 39% reduction of postoperative adhesion scores compared with the adnexa that did not receive the Interceed barrier. The use of Interceed resulted in a twofold increase in the number of adnexae without adhesions at the second-look laparoscopy.[222] Similar findings were obtained when oxidized regenerated cellulose was used to reduce adhesions after ovarian surgery.[223]

Uterine Factor Infertility

Congenital uterine anomalies impact reproductive and obstetric outcomes. In a systematic review and meta-analysis of 21 retrospective and 4 prospective studies involving 3477 women, only the septate uterus was associated with a reduced rate of spontaneous pregnancy (RR 0.89; 95% CI, 0.77 to 0.96). The probability of pregnancy following IVF was not affected by the common congenital uterine anomalies. The risk of spontaneous abortion was significantly increased in women with septate (RR 2.81), bicornuate (RR 2.40), and unicornuate (RR 2.10) uteri. Risk for preterm delivery before 37 weeks was increased for all congenital anomalies except for the arcuate uterus. The risk for malpresentation, for example breech presentation, in labor was significantly increased for all anomalies, but most markedly with septate (RR 4.35) or bicornuate (RR 4.65) uteri. The risk for fetal growth restriction was greatest with uterus didelphys or bicornuate or unicornuate uteri. The risk for placental abruption was increased for arcuate (RR 6.60) and septate (RR 4.37) uteri. A hysteroscopic resection of a uterine septum lowered the risk for miscarriage (RR 0.37) compared to untreated women with a septate uterus.[224] Among infertile women, submucus myomas and large endometrial polyps are thought to reduce fecundability and are generally resected using hysteroscopy.[225] Uterine factor infertility is discussed in detail in Chapters 13 and 26.

Cervical Factor Infertility

The cervix is an active participant in shepherding sperm from the vagina to the upper reproductive tract. In the normal cervix, the secreted cervical mucus has physicochemical properties that facilitate the transport of sperm. Congenital malformation and trauma to the cervix may impair the ability of the cervix to produce normal mucus.

Historically the postcoital test was used to assess sperm interaction with the cervical mucus, but it is rarely performed in modern fertility practice. There is little consensus on how to interpret the test. Some authorities suggest that a normal test requires more than 20 sperm per high-power field.[226] Other authorities conclude that the presence of a single sperm indicates a normal test.[227] The link between the results of a postcoital test and fertility potential is tenuous. In one study of the relationship between the postcoital test and fecundability, 20% of fertile women were observed to have one sperm or less per high-power field.[228] In another study, fecundability did not seem to be altered by the presence of between 0 and 11 sperm per high-power field.[21]

Dysplasia of the cervix is a common problem that is often treated with excision of cervical tissue infected with human papilloma virus. Recent epidemiological studies have reported that loop electrosurgical excision (LEEP) of cervical tissue is associated with cervical stenosis,[229] preterm delivery, and low-birth-weight infants.[230]

Endometriosis

The relationship between endometriosis and infertility and the treatment of infertility caused by endometriosis are reviewed in Chapter 25.

Uterine Leiomyomata

The impact of uterine leiomyomata on fertility is reviewed in Chapter 26.

Immunologic Factors and Recurrent Abortion

Recurrent abortion caused by autoimmune diseases, coagulopathies, and infections are discussed in Chapter 13.

Genetic Causes of Infertility

For many decades, it has been known that major chromosomal abnormalities are often associated with infertility. Women with 45,X (Turner syndrome) have premature depletion of the oocyte pool and are typically sterile. Translocations and interstitial deletions of the X chromosome are associated with premature ovarian failure, although the identity of the genes in these deletions remains to be established. In infertile men, Yq11 microdeletions are observed in about 5% of cases.[231] A major goal of reproductive scientists is to identify individual genes that are associated with infertility. Recently, many genes that influence fecundability have been identified.[232] Genes in which mutations affecting female fertility and fecundity have been identified include Galactose-1-phosphate uridyl transferase *(GALT)*,[233] the FSH receptor,[234-236] the LH receptor,[237] premutations in the *FMR1* (fragile X syndrome) gene,[238,239] the *BMP15* gene,[240] the *NR5A1* (steroidogenic factor 1) gene,[241] and the ataxia–telangiectasia *(ATM)* gene.[242] Mutations that disrupt oocyte function and cause female infertility include mutations in *ZP1*,[243] *TUBB8*[244] and *STAG3*, which both encode oocyte spindle proteins (see Chapter 8).[245] Development of low-cost methods for nucleic acid sequencing is rapidly changing the approach to genotype-phenotype studies of

infertile couples. Next-generation sequencing increases the ability to find "broken genes" that might cause or contribute to infertility. In clinical fertility practice, molecular genetic analysis of the number of CGG repeats in the *FMR1* gene (fragile X) to detect fragile X premutation carriers and karyotyping white blood cells to diagnose Turner syndrome are the genetic tests most frequently used to identify the cause of ovarian insufficiency.

Unexplained Infertility

◆ *Following an infertility evaluation, many infertile couples have no obvious cause for their infertility. Step-wise treatment of unexplained infertility with clomiphene-IUI and IVF will result in pregnancy for most couples where the female partner is less than 40 years of age.*

Unexplained infertility is diagnosed when a couple has failed to achieve a pregnancy after 12 months of attempting conception and has completed a thorough evaluation without finding a cause for the infertility.[246] The diagnosis of unexplained infertility rests heavily on the definition of what constitutes a thorough fertility evaluation. For many fertility specialists, a thorough evaluation includes documentation of the following findings:

- Adequate ovulation, using a midluteal phase serum progesterone determination greater than 3 ng/mL
- Tubal patency and normal uterine contour as determined by HSG, HyCoSy, or laparoscopy
- Normal semen analysis, demonstrating 15 million sperm per milliliter, greater than 32% motility, and greater than 4% normal morphology by strict criteria
- Adequate ovarian oocyte reserve, using either a cycle day 3 FSH determination (below 10 mIU/mL), a clomiphene challenge test (both cycle day 3 and 10 FSH measurements below 10 mIU/mL), AMH greater than 0.9 ng/mL, or AFC greater than 4

Most fertility specialists believe that laparoscopy is not a necessary component of a thorough infertility evaluation because it is expensive and seldom dramatically changes the approach to treatment. The majority of fertility specialists believe that laparoscopy should be reserved for use in selected cases of female infertility, including women with a history of severe pelvic pain consistent with endometriosis. A minority of specialists believe that laparoscopy is an important component of a thorough infertility evaluation because it identifies peritoneal adhesions and endometriosis lesions that may otherwise remain undetected.

In one large retrospective study of 495 infertile couples with normal ovulation, normal HSG, and normal semen analysis, laparoscopy was performed on all the female partners and 31% were diagnosed with either major pelvic adhesions and tubal disease (10%) or endometriosis (21%).[247] In a separate study, a cost-benefit analysis concluded that for couples with normal initial fertility tests, a laparoscopy to detect and treat endometriosis and peritoneal adhesions followed by expectant management was more cost effective than no laparoscopy plus IUI followed by superovulation IUI followed by IVF.[248] One approach is to limit the use of laparoscopy in the infertility evaluation to those women who have a high likelihood of having endometriosis or pelvic adhesions, such as women with a history of pelvic pain or a history of pelvic infection.

Many cases of unexplained infertility are probably caused by the presence of multiple factors (e.g., female partner 37 years of age or older, male partner with semen parameters in the low end of the normal range). Each of these factors on its own does not substantially reduce fertility; however, when more than one factor is present, fecundability is reduced. Subtle changes in follicle development, ovulation, oocyte function, the luteal phase, and sperm function have been reported in couples with unexplained infertility.[249] In some couples with unexplained infertility, the male partner has a semen analysis with sperm concentration and motility at the lower end of the normal range.[250]

When couples with unexplained infertility are treated with IVF, they demonstrate reduced oocyte fertilization and embryo cleavage rates compared with couples where tubal factor is the cause of the infertility. For example, in one study, the oocyte fertilization rate for tubal factor infertility and unexplained infertility were 60% and 52%, respectively. When couples with unexplained infertility are treated with IVF, they have a higher rate of complete fertilization failure than couples with tubal factor infertility (6% vs. 3%). As noted previously, women with patent fallopian tubes on HSG who are seropositive for chlamydia antibodies have lower fecundability than women who are seronegative.[190] These results suggest that couples with unexplained infertility probably have subtle functional abnormalities in oocyte, sperm, and tubal function.[251]

Empiric Treatment of Unexplained Infertility

The management of couples with unexplained infertility typically starts with treatments that consume few resources (lifestyle changes, timing of the intercourse to the fertile time of the menstrual cycle, expectant management, IUI, clomiphene, clomiphene plus IUI) and moves sequentially to treatments requiring proportionately greater resources (gonadotropin injections plus IUI or IVF), as shown in Fig. 22.13.[252] The rationale underlying this strategy is that treatment is initiated with low-cost, low-risk interventions; then, with each step in the program, interventions are initiated that use greater resources and carry more risk. This approach has been reported to be cost effective in the treatment of unexplained infertility.[253] The pace at which the staircase is

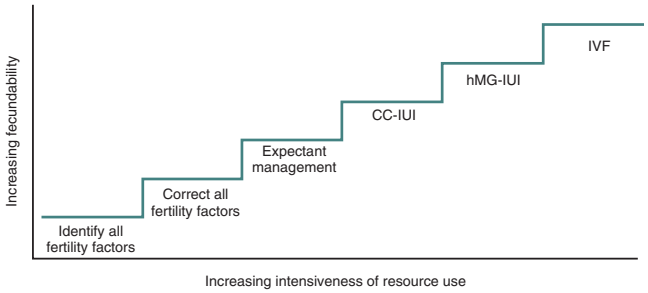

FIGURE 22.13 Staircase approach to empirical infertility treatment. For women over 35 years old, the first three steps in the algorithm should be rapidly completed. In women under 30 years old, more time can be spent on the first three steps in the staircase. *CC*, Clomiphene; *hMG*, human menopausal gonadotropins; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization.

climbed depends on many factors, including the age of the female partner, the duration of infertility, and the beliefs and values of the clinicians and patients.

Lifestyle changes can enhance the fertility of couples.[254,255] Lifestyle changes that can improve fertility include normalizing the BMI, ceasing smoking, reducing the use of caffeine and alcohol, reducing stress, avoiding excessive exercise, improving diet, and increasing the frequency of sexual intercourse at the fertile time of the cycle.[256,257] Lifestyle changes to enhance fertility have not been tested in high-quality clinical trials. Most of the evidence linking optimizing lifestyle choices and fertility are derived from epidemiological studies. Most epidemiological studies report that the magnitude of the impact of optimizing lifestyle choices on fertility is greater for the female partner than the male partner, but both partners should jointly participate in optimizing their reproductive health. Epidemiological studies indicate that for the female partner, cigarette smoking and excessive caffeine and alcohol consumption reduce fertility. Couples with unexplained infertility should be counseled to stop smoking cigarettes. The female partner should be counseled to reduce caffeine intake to no more than 250 mg daily (two cups of coffee) and to reduce alcohol intake to no more than four standardized drinks per week. The male and female partner should be guided to try to achieve an optimal BMI, ranging from 19 to 25 kg/m^2.[258,259]

Based on data from observational studies, dietary patterns appear to influence the ovulation rate in women and semen quality in men. In women, an increase in the frequency of normal ovulatory cycles is observed with the following dietary patterns: high intake of low-glycemic index food, low protein intake from animal sources, high protein intake from vegetable sources, high intake of fat from dairy products, and high iron intake.[260] A Mediterranean-type dietary pattern appears to optimize fertility potential.[261]

In the treatment of unexplained infertility, timing intercourse to the portion of the menstrual cycle with the greatest chance for conception is an important and inexpensive intervention that can increase fecundability.[262] Urine LH testing at home is commonly used to identify the LH surge which occurs 1 to 2 days before ovulation. The days of the cycle with the greatest probability of pregnancy with one episode of sexual intercourse are the days of ovulation, and the two days before ovulation.[263,264] Since the urine LH surge occurs 1 to 2 days before ovulation, it identifies in a prospective manner the fertile days of the cycle.

For young couples with unexplained infertility and a good prognosis, expectant management is a reasonable and cost-effective approach to treatment.[265-267] When couples with unexplained infertility are followed prospectively without active treatment, approximately 1% to 4% become pregnant each month. For couples with unexplained infertility and a fecundability less than 0.01 (poor prognosis couples), waiting to initiate treatment is not cost effective. For couples with unexplained infertility and a fecundability of 0.04 (good prognosis couples), expectant management with timing of intercourse to the fertile part of the cycle is cost effective, especially if the female partner is young. Fertility factors that improve prognosis in couples with unexplained infertility include female partner younger than 32 years of age, couple with less than 2 years of infertility, couples with a prior pregnancy, and semen analysis with sperm motility greater than 40%.[6] Effective fertility treatment for unexplained infertility must increase the pregnancy rate above this baseline fecundability of approximately 0.01 to 0.04. The age of the female partner influences the pregnancy rate associated with expectant management.[269] For women with unexplained infertility over 37 years of age, the pregnancy rate per cycle with expectant management is likely under 1%. For couples where the female partner is over 37 years of age, the ovarian oocyte pool declines rapidly. Delays in conception inevitably cause ovarian aging to become an increasingly important cause of the fertility problem. For women over 37 years of age, expectant management is not recommended.

Intrauterine Insemination

The IUI procedure consists of washing an ejaculated semen specimen to remove prostaglandins and other factors, and then concentrating the sperm in a small volume of culture media with a high protein concentration to enhance capacitation and the acrosome reaction. The sperm suspension is then injected directly into the upper uterine cavity using a small catheter threaded through the cervix. In one study of various methods used to prepare the sperm for IUI, the swim-up and Percoll gradient preparation techniques resulted in superior pregnancy rates compared with the simple wash, swim-down, or refrigeration/heparin techniques. IUI is timed to take place just prior to ovulation, typically using home urine LH monitoring. In couples reporting male infertility, IUI more than doubles the pregnancy rate compared with intracervical insemination or timed natural cycles (odds ratio [OR] 2.2; 95% CI, 1.4 to 3.4).[270] In one study of couples with mild male infertility, the pregnancy rate per cycle was 6.5% for IUI versus 3.1% for intracervical insemination or timed natural intercourse.[271] IUI also appears to be effective for couples with unexplained infertility.

In a large clinical trial sponsored by the National Institutes of Health, 932 infertile couples with unexplained infertility or stage I or II endometriosis were randomized to one of four treatment groups: intracervical insemination (ICI) of sperm, IUI, FSH injections plus ICI, or FSH injections plus IUI.[250] The purpose of the ICI was to be a control treatment that mimicked natural intercourse. The purpose of the IUI was to place a large number of sperm high in the uterus by passing the vagina and cervix. The purpose of the FSH injections was to stimulate multiple follicular development and ovulation, thereby increasing the number of oocytes available for fertilization in a single cycle (this type of treatment is explained later in this chapter). Most of the women in this study had either unexplained infertility or early stage endometriosis. The investigators reported that the per-cycle pregnancy rate in the group that received the control (ICI treatment) was 2%. This pregnancy rate is similar to expectant management. IUI treatment was associated with a 5% per-cycle pregnancy rate. The per-cycle pregnancy rates in the FSH-ICI and FSH-IUI groups were 4% and 9%, respectively. In this study, IUI was clearly effective for the treatment of unexplained infertility.[250] It should be noted that the fecundability in the control and IUI cycles were 0.02 and 0.05, respectively. Although IUI increases fecundability in couples with unexplained infertility, the therapeutic benefit is modest, especially compared to IVF.

Multiple procedure-related factors appear to influence the effectiveness of IUI. Most recent studies report that

one IUI per cycle results in a pregnancy rate similar to two IUI procedures per cycle.[272,273] In couples with a mild male factor problem, double IUI may increase the pregnancy rate.[274] Resting supine after the IUI procedure may also be associated with higher pregnancy rates than those in patients who ambulated soon afterwards.[275]

Clomiphene Citrate Monotherapy

Clomiphene monotherapy for the treatment of unexplained infertility is controversial. In women with spontaneous ovulation, clomiphene often stimulates multifollicular development, the ovulation of two follicles and increased luteal progesterone secretion. Mild ovarian stimulation may increase fecundability in couples with unexplained infertility. In a 2000 meta-analysis, including 11 trials of clomiphene treatment for women with unexplained infertility, the authors concluded that clomiphene was superior to placebo or no treatment. The odds ratio for clinical pregnancy per clomiphene treatment cycle was 2.5 (95% CI, 1.35 to 4.62).[276] In one trial where 118 female partners from couples with unexplained infertility were randomized to treatment with placebo or CC (100 mg daily, cycle days 2 to 6), the per-cycle pregnancy rates were 5% and 7%, respectively ($P < .05$).[277] In another trial, clomiphene treatment resulted in a significantly increased pregnancy rate compared to placebo treatment (19% vs. 0%).[278] However, in a 2010 meta-analysis involving seven trials, clomiphene was reported to be no more effective than no treatment (OR 0.79; 95% CI, 0.45 to 1.38).[279] In one recent randomized trial of expectant management versus clomiphene for unexplained infertility, the cumulative pregnancy rates after 6 months of treatment were 17% and 14%, respectively, demonstrating no efficacy for clomiphene monotherapy of unexplained infertility.[280]

Many specialists believe that clomiphene monotherapy should not be used in the treatment of unexplained infertility.[281] It is likely that clomiphene is overprescribed for the treatment of infertility. In a prospective study of 10,036 women with infertility, 94% reported taking clomiphene for fertility treatment.[282] Given that tubal disease and male factor cause infertility in greater than 40% of couples, it seems unlikely that clomiphene treatment was warranted in all these women.

Clomiphene Plus Intrauterine Insemination

The combination of clomiphene (increases the rate of double ovulation) plus IUI, which places a large number of motile sperm high in the female reproductive tract, may successfully treat mild abnormalities of ovulation, oocyte function, and sperm function in couples with unexplained infertility. In one study, 67 couples were randomized to treatment with clomiphene plus IUI or placebo. The pregnancy rate per cycle was 3.3% for the control group and 9.5% for the clomiphene plus IUI group.[283] For clomiphene-plus-IUI cycles, timing of the IUI is usually based on home urine LH measurement. Timing IUI with home urine LH measurement or exogenously administered hCG is associated with a similar pregnancy rate, but hCG administration is associated with greater cost and an increased risk of OHSS.[284] The pregnancy rate with clomiphene-IUI decreases with advancing age of the female partner (Fig. 22.14). Among 4199 clomiphene-IUI cycles, the cumulative pregnancy rate for women younger than 35, 35 to 37, 38 to 41, 41 to 42, and older than 42 years of age were 24%, 19%, 15%, 7.4%, and 1.8%, respectively.[285]

Ovarian stimulation with clomiphene, letrozole, and gonadotropin combined with IUI for the treatment of unexplained infertility has been studied in a large clinical trial involving 900 couples. After 4 cycles of treatment, the cumulative live births observed in this trial were 23%, 19%, and 32% with clomiphene-IUI, letrozole-IUI, and gonadotropin-IUI, respectively.[286] There was no significant difference in the live birth rate between clomiphene and letrozole, but gonadotropin-IUI resulted in more live births than either clomiphene-IUI or letrozole-IUI. The multiple birth rate for clomiphene-IUI, letrozole-IUI, and gonadotropin-IUI were 6%, 14%, and 32%, respectively.

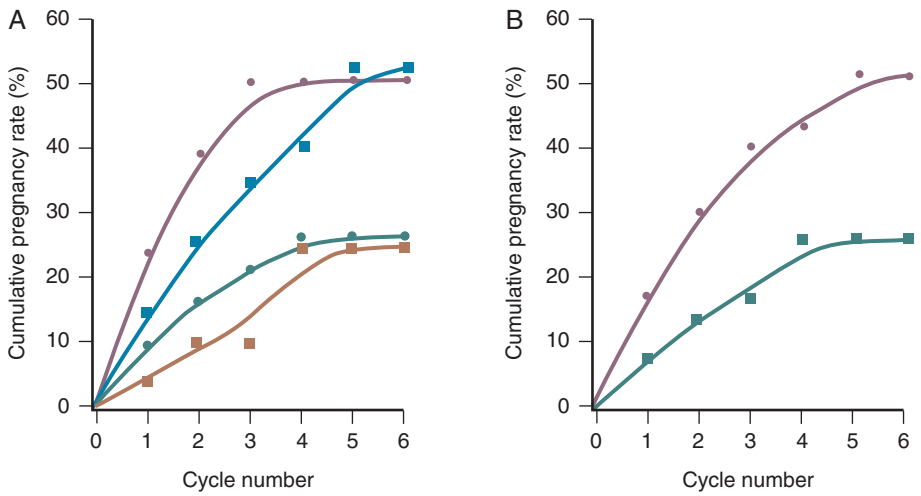

FIGURE 22.14 Cumulative pregnancy rates by Kaplan-Meier life-table analysis for 290 infertile couples undergoing clomiphene intrauterine insemination therapy stratified by the age of the female partner. (A) Ages of women: *purple circles,* under 30; *blue squares,* 31 to 35; *green circles,* 36 to 40; *brown squares,* 41 or over. (B) Ages of women: *circles,* under 35; *squares,* over 35. *(From Agarwal SK, Buyalos RP: Clomiphene citrate with intrauterine insemination: is it effective therapy in women above the age of 35 years?* Fertil Steril *65:759–763, 1996, with permission.)*

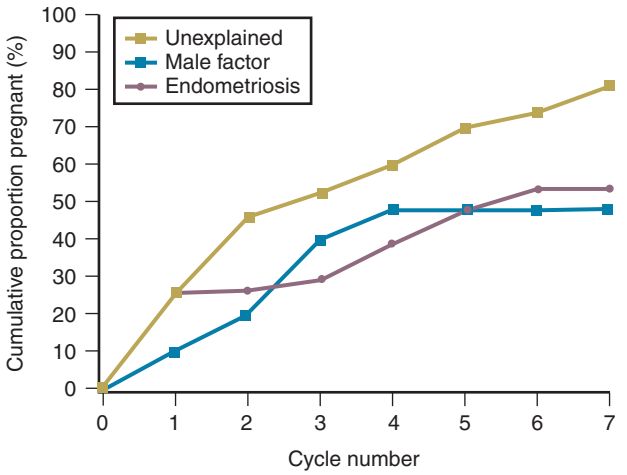

FIGURE 22.15 Cumulative pregnancy rate for gonadotropin-intrauterine insemination treatment for various fertility conditions: unexplained, early-stage endometriosis, and male factor. *(From Nulsen JC, Walsh S, Dumex S, Metzger DA: A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility.* Obstet Gynecol *82:780–786, 1993, with permission.)*

Gonadotropin Injections and Gonadotropin Injections Plus Intrauterine Insemination

Both gonadotropin injections alone and gonadotropin injections plus IUI increase fecundability in women with unexplained infertility. Gonadotropin injections plus IUI also appears to increase fecundability in infertile women with stage I or II endometriosis and in infertile men with semen abnormalities (Fig. 22.15).[287] In one study, 932 infertile couples with unexplained infertility or stage I or II endometriosis were randomized to one of four treatment groups: ICI, IUI, FSH injections plus ICI, or FSH injections plus IUI. The pregnancy rate in the control, the ICI group, was 2% per cycle. In the FSH-plus-ICI and the FSH-plus-IUI groups, the pregnancy rate per cycle was 4% and 9%, respectively.[250] The main complications of the use of FSH injections in the treatment of infertility in women with unexplained infertility are an increase in the rate of multiple gestations and ovarian hyperstimulation. Of the ongoing pregnancies in this study, 3% were quadruplets, 5% were triplets, and 20% were twins. In a trial of clomiphene-IUI and gonadotropin-IUI, 330 couples with unexplained infertility, mild male factor or stage I or II endometriosis were randomized. The live birth rate for a single cycle of clomiphene-IUI and gonadotropin-IUI were 9% and 14%, respectively.[288] In another study of gonadotropin injections with or without IUI, Serhal et al.[289] randomized 62 couples with unexplained infertility to receive IUI alone, gonadotropin injections alone, or gonadotropin injections plus IUI. The per-cycle pregnancy rate was 2.2% for IUI alone, 6.1% for gonadotropin injections alone, and 26% for gonadotropin injections plus IUI. Similar results have been reported by other investigators.[290-292]

Although there is evidence for the efficacy of gonadotropin with or without IUI for the treatment of unexplained infertility, many authorities highlight the increased risk of multiple gestation with these therapies, and advise that the use of gonadotropin or gonadotropin-IUI treatment for unexplained infertility should be very limited.[293-295] If good prognosis couples with unexplained infertility can be counseled to continue to try to get pregnant on their own, and not pursue gonadotropin therapy, many will become pregnant spontaneously.[296] In a recent trial comparing the three-step sequential treatment protocol (clomiphene-IUI, followed by gonadotropin-IUI, followed by IVF) versus a two-step sequential treatment protocol (clomiphene-IUI followed by IVF) the clinical utility of the gonadotropin-IUI was poor.[297] In this study, the per-cycle pregnancy rate for clomiphene-IUI was 7.6%, gonadotropin-IUI 9.8%, and IVF-31%. Since gonadotropin-IUI is expensive, and much less effective than IVF, the most cost-efficient approach was the two-step sequential treatment plan of clomiphene-IUI followed by IVF. The two-step approach was approximately 15% less expensive per live birth than the traditional three-step approach. Over the past 30 years, the IVF live birth rate per cycle has increased from 5% to 40%. As the pregnancy rate per cycle of IVF increases, the clinical utility of FSH-IUI decreases, because IVF becomes a more cost-effective method of achieving a pregnancy.

In Vitro Fertilization

IVF is effective in the treatment of unexplained infertility.[298] In one randomized trial, 116 couples with unexplained infertility and a poor prognosis for spontaneous pregnancy were randomized to single embryo transfer IVF or FSH-IUI. The live birth rate was 22% and 7% for IVF and 1 cycle of FSH-IUI, respectively. However, when the women in the FSH-IUI group completed 3 cycles of FSH-IUI, the cumulative life birth rate was 21%. The multiple pregnancy rate was 14% in the single embryo transfer IVF group and 25% in the FSH-IUI group.[299] In a clinical trial of clomiphene-IUI, FSH-IUI and IVF, 154 couples with unexplained infertility were randomized to 2 cycles of each treatment. The cumulative clinical pregnancy rate with clomiphene-IUI, FSH-IUI, and IVF were 22%, 17%, and 49%, respectively.[300] IVF as a treatment for infertility is covered in Chapter 31.

Pace of Escalation in the Treatment of Unexplained Infertility

As noted above, couples with unexplained infertility and a good prognosis may be offered expectant management, and if that is not successful, they may proceed from low-resource interventions, such as clomiphene-IUI, to resource-intensive treatments, including FSH-IUI or IVF. For couples with unexplained infertility and a poor prognosis (female age >37 years, >2 years of infertility) it may be preferable to more rapidly move from low-resource interventions to IVF. Studies of cohorts of infertility patients report that after 2 or 3 cycles of any one treatment, such as IUI, CC-IUI, or FSH-IUI, the pregnancy rate tends to decline. In general, after 3 cycles of any one treatment, it is recommended to consider advancing to the next step in the treatment algorithm (Fig. 22.16).[301]

Environmental Exposures Associated With Infertility

The impact of environmental factors on reproduction is discussed in Chapter 19.

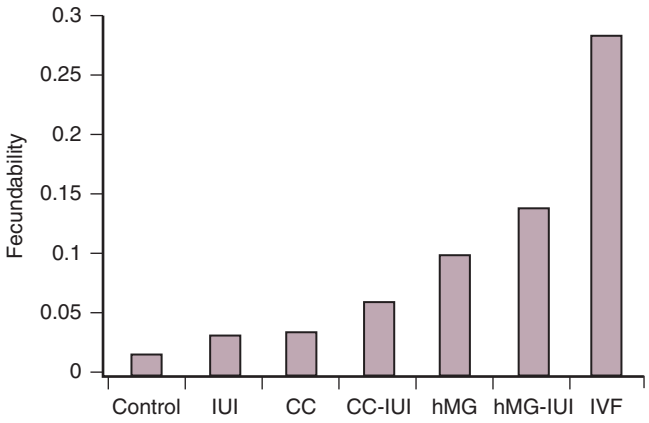

FIGURE 22.16 Fecundability associated with empirical treatment of unexplained infertility. *CC-IUI*, Clomiphene citrate plus intrauterine insemination; *Control*, no treatment; *hMG*, human menopausal gonadotropin; *hMG-IUI*, human menopausal gonadotropin plus intrauterine insemination; *IDI*, intrauterine insemination; *IVF*, in vitro fertilization and embryo transfer.

Contraindications to Infertility Treatment

An adage in medicine is "first do no harm." Fertility treatments have the potential to significantly harm women and the children born following fertility treatments. Counterbalancing the potential harm caused by fertility treatment is the right of patients to request treatments to achieve an important health goal, even if some risks are involved. There are a limited number of diseases that are an *absolute contraindication* to fertility treatment. When pregnancy occurs in a woman with Eisenmenger syndrome, there is a 50% risk of maternal death.[302] Consequently, fertility treatment is contraindicated in women with Eisenmenger syndrome, regardless of the wishes of the woman. Many authorities strongly caution against fertility treatment in women with Turner syndrome due to an approximately 1% to 2% risk of aortic dissection.[303] However, many high-risk obstetricians will not advise against pregnancy in these women if their aortic root diameter is not dilated. The age of the female partner is a factor that must always be considered when recommending fertility treatment. There must be an age of the female partner where fertility treatment poses too great a risk for mother and child, such as age greater than 55 years.[304] Population studies raise the concern that oocyte donation to older women is associated with an increased maternal mortality rate.[305]

There are many clinical situations where there is a relative contraindication to fertility treatment. Most of these contraindications are due to obstetrical considerations: the pregnancy poses serious risks during the pregnancy or at the time of delivery. For example, a woman with massive pelvic adhesions and a frozen pelvis can achieve a pregnancy with IVF. But at delivery, if an emergency cesarean delivery is necessary, a bowel resection may be needed to gain access to the uterus to complete the cesarean delivery. The BMI of the female partner is of particular concern to obstetricians because of the high risk of difficult delivery. Obstetricians and fertility specialists have not reached a consensus about the wisdom of fertility treatment in women with a BMI greater than 60 kg/m^2. Many fertility specialists believe that delaying fertility treatment in a 40-year-old infertile woman with a BMI greater than 60 kg/m^2 is unethical because her ovarian follicle pool is nearly depleted.[306] Delaying her fertility treatment for additional attempts at weight loss may result in further depletion of her ovarian follicle pool and result in sterility. In contrast, some obstetricians conclude that in women with a BMI greater than 60 kg/m^2 the risks of pregnancy, including a high rate of difficult delivery, make it dangerous to use fertility treatments.[307]

Infertility Treatment and Pregnancy Outcomes

Many observational studies report that pregnancy following IVF is associated with increased risks of multiple gestations, congenital anomalies, preterm deliveries, low birth weights, and abnormal placentations. Even in a singleton pregnancy following IVF, there is an increased risk of fetal growth restriction, preeclampsia, prematurity, and perinatal mortality. However, infertility itself may be associated with these risks, regardless of whether an infertile woman becomes pregnant spontaneously or following fertility. For example, in a study from the Danish National Birth Cohort, fetal birth weight was compared in 51,000 singletons born of fertile couples, 5787 born of infertile couples *conceiving naturally*, and 4317 born of infertile couples after *fertility treatment*. Maternal age and BMI were greater in the infertile couples. After adjusting for these variables and for smoking status, both the infertile couples who conceived naturally and those who conceived after fertility treatments had an increased risk of having a baby with a birth weight less than the fifth percentile compared with noninfertile women (6% vs. 4.2%).[308] Similar findings have been reported in studies from Finland; subfertile women who conceived spontaneously and those who conceived following fertility treatment had a similar rate of preterm birth, low birth weight, and need for neonatal intensive care.[309] A study from Norway examined the birth outcomes in 2546 women who had one child by IVF and one child conceived without treatment.[310] Compared to the entire Norwegian population, IVF conceptions were associated with a lower mean birth weight (–25 g), shorter duration of gestation (–2 days), and increased risk for small for gestational age birth weight (OR 1.26; 95% CI, 1.10 to 1.44). However, when compared to their matched sibling who was conceived without fertility treatment, there was no difference in birth weight, length of gestation, or risk for small-for-gestational-age birth weight. The biological processes causing infertility may have a larger impact on pregnancy outcome and fetal growth than the infertility therapy itself.[311] Most studies of birth outcome following fertility therapy have focused on IVF pregnancies. One large retrospective study examined birth outcomes in fertile women, subfertile women who conceived without treatment, and subfertile women who conceived with ovulation induction or ART.[312] Of note, the subfertile women were significantly older and had higher BMI than the fertile women. In pregnancies with a singleton gestation, the subfertile women had a significantly increased risk for preeclampsia, antepartum hemorrhage, cesarean delivery, operative vaginal delivery, preterm birth, low birth weight, small for gestational age, and perinatal loss. However, among the subfertile women, spontaneous

conception and conception following ovulation induction or ART had similar birth outcomes. This study suggests that subfertility, per se, is a major contributor to the observed difference in birth outcomes observed between fertile and subfertile women. Of note, early childhood development and growth appear to be similar in children born of fertile mothers or infertile mothers who had any fertility treatment.[313,314]

Adoption

A difficult decision in fertility treatments is deciding when to cease active interventions designed to increase fecundability. Throughout the process of fertility treatment, it is prudent to raise the issue of when to cease active intervention and to offer adoption as an alternative method of building a family. It may be useful for couples to simultaneously explore the option of adoption while they are undergoing fertility therapy. If the fertility therapy fails, adoption may help couples cope with the symbolic loss created by their infertility.

Psychosocial Aspects of Infertility

Many observational studies report that stress is associated with infertility. In turn, the treatment of infertility can cause stress. Reducing stress prior to initiating intensive fertility treatments may improve the ability of the couple to successfully complete the treatments recommended.[315] For example, in one study, 151 women were given a standardized test to evaluate their moods, sense of optimism, social support networks, self-perceived stress, and methods of coping prior to undergoing IVF. Elevated levels of baseline stress were associated with fewer oocytes retrieved and fertilized and fewer embryos.[316] No definitive clinical trial demonstrates that reducing stress prior to infertility treatment improves pregnancy rates. However, in one small clinical trial, Domar et al. reported that treatment of infertile women with a support group or a structured relaxation program was associated with better pregnancy rates with infertility treatment than those observed in a control group.[317]

Infertility and the associated diagnostic and therapeutic procedures can produce substantial stress for both male and female partners, and disrupt their relationship with each other. Inherently, diagnostic and therapeutic procedures offer hope for an imminent successful conception, but each subsequent menstrual cycle rekindles the feeling of loss. The repetitive cycles of hope and loss can be very stressful for couples with infertility.[318] Infertility may be perceived by the couple as a loss that is difficult to grieve because the absence of fertility is somewhat intangible. Infertility may be especially stressful for those couples where the cause of the infertility is difficult to identify.[319] The classic progression of emotions related to a loss is often expressed by the infertile couple.[320] These include the feelings of disbelief and surprise, denial, anger, isolation, guilt, grief, and resolution. For many couples, the female partner bears a disproportionate degree of responsibility for the loss symbolically represented by infertility.

In a Dutch study of 51,221 women with infertility, the risk of suicide was increased among infertile women who did not have a child following fertility treatment compared to infertile women who conceived (hazard ratio 2.43; 95% CI, 1.38 to 3.71).[321] A Swedish study reported that women with depression and/or anxiety had reduced odds of pregnancy and live birth following IVF treatment.[322] Clinicians providing fertility care should monitor the impact of the fertility problem, diagnostic tests, and treatment on the patient's mental health.

Patients report that it is important that they be treated with respect and dignity and have all treatment options thoroughly and fairly presented. Patients wanted their clinicians to recognize their distress and respond in an empathic manner.[323,324] In most surveys, patients report that they are highly satisfied with the care provided by their fertility clinicians.[325]

Social and Ethical Issues

Medicine is an ethical profession that has long adhered to basic principles of human rights: respect for the dignity of human life; the right of an individual to participate in decisions that affect their health; an unwavering dedication to seek good and to avoid unnecessary harm; and a commitment to treat the patient fairly. Fertility practitioners also have an ethical obligation to protect the security of the human genetic material in their custody. Most ethicists are in agreement that the inviolability of each human precludes any medical intervention without the individual's consent. Free and informed consent is the cornerstone of ethical medical practice. Practices that are deceptive or could have the appearance of being deceptive undermine the credibility of clinicians in the fertility profession. Embryonic development is a continuous biological process. Current law tends to assign gradually increasing rights to the developing fetus. A human does not acquire full legal identity until birth, but is offered some legal protection as a fetus in utero (e.g., restrictions on legal abortion in the third trimester). Modern society is not unified on the point in the developmental process where the embryo or fetus becomes a unique individual with full rights to inviolability and inalienability. This disagreement, which is most obvious in the debate over abortion, will make it difficult to reach consensus on the ethics of certain types of fertility research, such as that performed on discarded embryos. However, most practitioners and ethicists are in agreement that cloning of humans is not ethical.

Insurance Against Female Infertility Due to Advancing Age

Numerous studies have reported a decline in pregnancy rate with advancing maternal age, largely due to a decrease in the number and quality of ovarian oocytes. Due to societal changes, there is an increase in the proportion of women choosing to delay childbearing until after age 35 years. Some assurance against female infertility due to advancing age can be obtained through cryopreservation of oocytes or embryo cryopreservation. Embryo cryopreservation involves many of the steps of in vitro fertilization, including stimulation of multiple follicles with FSH, prevention of premature LH surges with a GnRH analogue, triggering of the process of ovulation, retrieval of oocytes, fertilization with sperm, and cryopreservation of embryos. The embryos are thawed and transferred to the uterus at a later time that is optimized for the woman's family building plans. Women without a partner may not want to fertilize the oocytes retrieved in

the process, delaying the choice of the sperm that will be used for fertilization. For these women, oocyte cryopreservation is the optimal plan. For most women who do not have a committed partner or who are not interested in using donor sperm, oocyte cryopreservation is an attractive option for fertility preservation. Oocyte cryopreservation is a clinical standard of care for women concerned about female infertility due to advancing age and interested in fertility preservation.[326] Although considered the standard of care, there are few large case series of pregnancy and childhood outcomes following successful oocyte cryopreservation performed for fertility preservation.[326] In one series of 1027 live births following the use of thawed oocytes to achieve pregnancy, the obstetric and newborn outcomes were similar to those observed in live births derived from the use of fresh oocytes.[327] Theoretically, ovarian tissue cryopreservation could be used as insurance against female infertility caused by advancing age. However, this procedure is generally only used in women at risk of ovarian failure from cytotoxic medications or radiation treatment.[328]

The technology for mature oocyte cryopreservation has been greatly advanced by the use of vitrification techniques.[329] In a study of 1468 women who had vitrification of mature oocytes, 137 women returned for oocyte thawing, fertilization, and embryo transfer resulting in a live birth rate per woman of 50% for women 35 years of age or younger and 23% for women 36 years of age or older.[329] These rates are comparable to the pregnancy rates achieved with cryopreserved and thawed embryos. It is important to note that in this large case series, at the time of publication only 9% of the women who underwent oocyte cryopreservation returned to use their frozen oocytes.

Counseling of women about the benefits, risks, and costs of oocyte cryopreservation to ensure against female infertility due to advancing age is complex. The age of the woman is an important factor guiding the counseling. The highest probability of live birth following oocyte cryopreservation occurs for women 35 years of age or younger. In addition to age, assessment of markers of ovarian reserve, including antimüllerian hormone concentration, antral follicle count, and day three FSH and estradiol concentration may help guide counseling. Oocyte cryopreservation in women 30 years of age or younger increases the probability that the oocytes will never be used to achieve a pregnancy because the woman will eventually decide to remain childless or will conceive without using the cryopreserved oocytes.[330] Counseling about oocyte cryopreservation is likely best focused on women in the age range of 30 to 35 years and in younger women known to have a diminished oocyte pool. A calculator that provides information about the relationship among age, number of oocytes retrieved, and probability of achieving a live birth is available on line (https://www.mdcalc.com/bwh-egg-freezing-counseling-tool-efct).[331] The calculator predicts that if 10 oocytes are cryopreserved for women 30 and 37 years of age, the probability of achieving one live birth using thawed oocytes is 69% and 50%, respectively. Societal trends are likely to support the continued development and greater use of oocyte cryopreservation as a means to protect against female infertility due to advancing age.

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