# 40 Infertility

## Etiology, Diagnostic Evaluation, Management, Prognosis

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KEY POINTS

- Infertility is considered to be a disease and affects approximately 7% of all U.S. couples of reproductive age—more than 7 million women in the United States.
- A systematic evaluation of factors involved in infertility should be carried out rapidly, along with markers of ovarian reserve (antral follicle count, antimüllerian hormone); this will help frame the discussion with couples as to how best to proceed with treatment.
- The prognosis for fertility after tubal reconstruction depends on the amount of damage to the tube and the location of the obstruction. Mild abnormalities of the proximal tube may be treated with selective catheterization/cannulation under fluoroscopy. Large hydrosalpinges (distal disease) are best treated by salpingectomy and in vitro fertilization (IVF).
- In women with unexplained infertility, the use of controlled ovarian stimulation (COS) and intrauterine insemination (IUI) with clomiphene/IUI or gonadotropins/IUI yields monthly fecundity rates of approximately 8% to 10% (at least doubling the baseline rate) and should be the initial treatment for unexplained infertility. Use of gonadotropins does not offer a major advantage over clomiphene and carries more risks in terms of hyperstimulation and multiple pregnancies.
- After three to six cycles of COS/IUI, IVF should be offered as the next step, and IVF should be the primary therapy in women around age 40.

## INFERTILITY AND NATURAL CONCEPTION

The term ***infertility*** is generally used to indicate that a couple has a reduced capacity to conceive compared with the mean capacity of the general population. In a group of normally fertile couples, the monthly ability to get pregnant, or ***fecundability***, is approximately 20% (0.02). Analysis of data from presumably fertile couples who stop using contraception to conceive is depicted in Fig. 40.1, with both the actual and theoretical time trends. (Hull, 1985). **The 20% is an average number and can be as high as 25% for the first 3 months of trying to conceive, but then decreases** after that for the following months going forward (Leridon, 1984) (Table 40.1). As time goes on, during the fourth, fifth, and sixth years of attempting to conceive, only 48%, 42%, and 37% of nonpregnant women conceive without treatment. These data are highly influenced by age, which will be discussed later.

The definition of infertility is the inability of a couple to conceive after 1 year of trying. This timeline is relevant to help determine when an infertility investigation should begin. In women older than 35 years, this timeline should be after 6 months of trying. An early investigation is also warranted if any of the following is present: oligomenorrhea or amenorrhea; known tubal obstruction, uterine disease, or severe endometriosis; or known male factor infertility (Practice Committee ASRM, 2012a).

The World Health Organization (WHO) has defined infertility as a disease and a significant cause of disability (warranting evaluation and treatment) (see www.who.int/reproductivehealth/topics/infertility/definitions). Clearly, infertility is a cause of major distress for couples and should be assessed thoroughly and not neglected; and as with other disorders, counseling and support groups should be available in the clinical setting.

## INCIDENCE OF SUBFERTILITY AND INFERTILITY

**Approximately 6% to 7% of all reproductive-age women (15 to 44 years) in the United States are considered to be infertile** according to statistics from the Centers for Disease Control and Prevention (CDC). The number of women in this age group who have ever used infertility services has been estimated to be 12% or 7.3 million women in the United States.

## INFERTILITY AND AGE

Data from both older and more recent studies have indicated that **the percentage of infertile couples increases with increasing age of the female partner.** Analysis of data from three national surveys in the United States has revealed that the percentage of presumably fertile married women not using contraception who failed to conceive after 1 year of trying steadily increased from ages 25 to 44 years (Menken, 1986) (Table 40.2). Data from a study of presumably fertile nulliparous women married to husbands with azoospermia who underwent donor artificial insemination revealed that the percentage who conceived after 12 cycles of insemination declined substantially after age 30 (Schwartz, 1982) (Table 40.3). This older, classic study used fresh semen; currently, only frozen donor sperm is used, which does not achieve as favorable pregnancy rates. Decreasing fecundability with age is even more pressing in this context. With in vitro fertilization (IVF), data from the Society for Assisted Reproductive Technology (SART) in the United States indicate that the percentage of deliveries per oocyte retrieval procedure is 43.4% in women younger than 35, 25.4% by ages 38 to 40, 14% by ages 41 to 42 years, and only 5% in women older than 42 years (https://www.cdc.gov/art/artdata/index.html).

In general terms, approximately one in seven couples are infertile if the wife is 30 to 34, one in five is infertile if she is 35 to 40, and **one in four is infertile if she is aged 40 to 44 years.** Another way to interpret these data is to state that compared with women aged 20 to 24 years, fertility is reduced by 6% in the next 5 years, by 14% between ages 30 and 34, by 31% between ages 35 and 39, and to a much greater extent after age 40. Of interest is the finding that the most common diagnostic category among

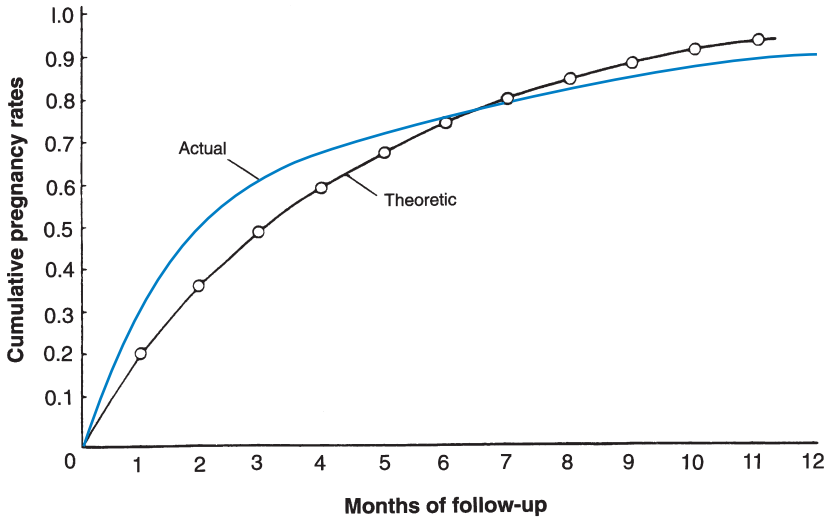



**Fig. 40.1** Curve of theoretic time to pregnancy in women with a monthly fecundability of 0.2 *(open circles)* and curve of actual time to pregnancy in fertile women discontinuing contraception *(solid line).* (Open circle data from Hull MG, Glazener CM, Kelly NJ, et al. Population study of causes, treatment, and outcome of infertility. *Br Med J.* 1985;291(6510):1693-1697. Solid line data from Murray DL, Reich L, Adashi EY. Oral clomiphene citrate and vaginal progesterone suppositories in the treatment of luteal phase dysfunction: a comparative study. *Fertil Steril.* 1989;51(1):35-41.)

**TABLE 40.1** Incidence of Conception Over Time among Nonsterile Couples with Mean Fecundability of 0.2

| | Couples Not Yet Having Conceived | | |
|---|---|---|---|
| **Months without Conception** | **Proportion (%)** | **Mean Fecundability** | **Proportion (%) of Couples Who Will Conceive (within 12 mo)** |
| 0 | 100.0 | 0.20 | 86.0 |
| 6 | 31.9 | 0.14 | 77.0 |
| 12 | 14.0 | 0.11 | 69.2 |
| 24 | 4.3 | 0.08 | 57.0 |
| 36 | 1.9 | 0.06 | 48.2 |
| 48 | 1.0 | 0.05 | 41.7 |
| 60 | 0.6 | 0.04 | 36.7 |

Modified from Leridon H, Spira A. Problems in measuring the effectiveness of infertility therapy. *Fertil Steril.* 1984;41(4):580-586.

**TABLE 40.2** Married Women Who Are Infertile, by Age*

| Age (yr) | Infertile (%) |
|---|---|
| 20-24 | 7.0 |
| 25-29 | 8.9 |
| 30-34 | 14.6 |
| 35-39 | 21.9 |
| 40-44 | 28.7 |

*From three national U.S. surveys.
From Menken J, Trussell J, Larsen U. Age and infertility. *Science.* 1986;233:1389-1394.

**TABLE 40.3** Pregnancy Rates by Age at 1 Year in Normal Women with Azospermatic Husbands after Donor Insemination

| Age (yr) | Pregnancy Rate (%) |
|---|---|
| <25 | 73.0 |
| 26-30 | 74.1 |
| 31-35 | 61.5 |
| 36-40 | 55.8 |

From Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. *N Engl J Med.* 1982;306(7):404-406.

women undergoing IVF in the United States in the most recent survey cited previously is diminished ovarian reserve: 17% of cycles; which is a characteristic of older women undergoing treatment (https://www.cdc.gov/art/artdata/index.html).

## CAUSES OF INFERTILITY

The exact incidence of the various factors causing infertility varies among different populations and cannot be precisely determined. Collins reported that among 14,141 couples in 21 publications, ovulatory disorders occurred 27% of the time; male factor, 25%; tubal disorders, 22%; endometriosis, 5%; other, 4%; and unexplained factors, 17% (Collins, 1995a). It has not been shown that other abnormalities, such as antisperm antibodies, luteal phase deficiency, subclinical genital infection, or subclinical endocrine abnormalities such as hypothyroidism or hyperprolactinemia in ovulatory women, are true causes of infertility. No prospective randomized studies have demonstrated that treatment of these latter entities results in greater fecundability than without treatment. If any of these do cause infertility, they do so infrequently. With current techniques of investigation, it is **not possible to diagnose the cause of infertility in up to 20%** of couples, and they are considered to have **unexplained infertility**.

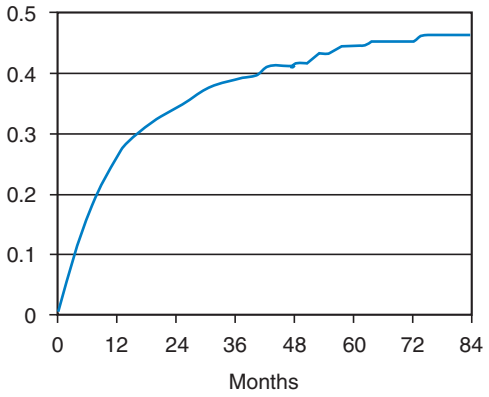



**Fig. 40.2** Cumulative rate of conceptions leading to live birth. Couples (873) remained untreated throughout follow-up; cumulative rate of live birth conception at 36 months was 38.2% (95% confidence interval, 34.2 to 42.3). (Modified from Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. *Fertil Steril.* 1995;64(1):22-28.)

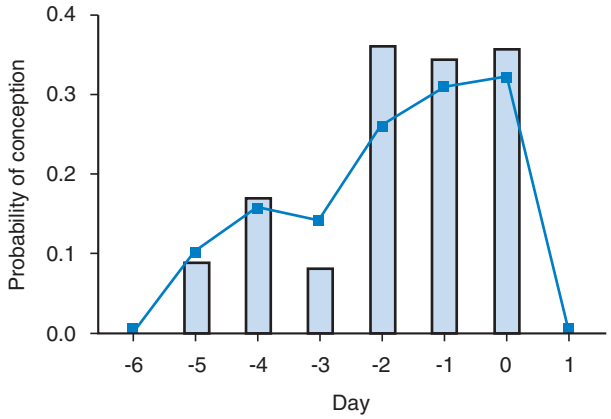



**Fig. 40.3** Probability of conception on specific days near the day of ovulation. The *bars* represent probabilities calculated from data on 129 menstrual cycles in which sexual intercourse was recorded to have occurred on only a single day during the 6-day interval ending on the day of ovulation (day 0). The *solid line* shows daily probabilities based on all 625 cycles, as estimated by the statistical model. (From Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation: effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med.* 1995;333:1517-1521.)

After a rigorous investigation, other reports have suggested this figure to be as low as 10%; however, it is unclear if subtle abnormalities, as noted, have much to do with infertility. Also, **most couples with unexplained infertility are subfertile rather than infertile, and some couples are able to conceive without treatment**, although it may take several years. A live birth rate among 873 infertile couples in several Canadian centers has been observed without treatment. The cumulative live conception rate was 38.2% at 3 years and 45% after 7 years (Collins, 1995b) (Fig. 40.2). Among the total group with the diagnosis of unexplained infertility who received no treatment, one-third had a live birth during the first 3 years of observation without treatment.

## DIAGNOSTIC EVALUATION

The diagnostic evaluation of infertility should be thorough and completed as rapidly as possible. During the initial interview, the couple should be informed about normal human fecundity and how these probabilities decrease with increasing age of the female partner and with the duration of infertility. The various tests in the diagnostic evaluation and why they are performed should be thoroughly explained. The available therapies and prognosis for treatment of the various causes of infertility should also be included in the dialogue. **The couple should be informed that after a complete diagnostic infertility evaluation, the cause for infertility cannot be determined in a large group of couples.** For many couples, the reduced fecundability can be suggested to be age related. Methods to increase the fecundity of couples with a normal diagnostic evaluation, such as *controlled ovarian stimulation* (COS) and intrauterine insemination, and the possibility of IVF should be covered.

Each couple should be instructed about the optimal time in the cycle for conception to occur and should be encouraged to have intercourse on the day before ovulation. Unless the husband has oligozoospermia (oligospermia), daily intercourse for 3 consecutive days at midcycle should be encouraged. When ovulation is more precisely determined, as with luteinizing hormone (LH) monitoring (discussed later), intercourse should occur for 2 consecutive days around the LH surge. Because the egg disintegrates less than 1 day after it reaches the ampulla of the tube, it is best that sperm be present in this area when the egg arrives so that fertilization can occur. Because normal sperm retain their fertilizing ability for up to 72 hours, it is preferable to have sperm in the tube before the arrival of the oocyte.

A study was performed by Wilcox and coworkers of fertile couples who stopped contraception to conceive and recorded the cycle day when they had sexual intercourse. Hormone analysis was performed to determine the day of ovulation. None of the women became pregnant in the group of couples who had intercourse after ovulation occurred**. The pregnancy rate was approximately 30% if intercourse occurred on the day of ovulation, as well as 1 and 2 days before ovulation.** The pregnancy rate was approximately 10% if coitus occurred 3, 4, or 5 days before ovulation. No pregnancies occurred when intercourse took place 6 days or more before ovulation (Wilcox, 1995) (Fig. 40.3). It is therefore considered optimal to perform insemination or have sexual intercourse on the day before ovulation.

Because peak levels of LH occur 1 day before ovulation, measurement of LH by urinary LH immunoassays is the best way to determine the optimal time to have intercourse or an insemination. Tests that measure LH in a random daily urine specimen are usually more convenient for planning natural or artificial insemination than tests that detect LH in the first morning urine specimen. **Ovulation most commonly occurs on the day after the detection of LH in a random specimen (12 to 24 hours later)**, and it occurs on the day when LH is detected in the first morning specimen, which contains urine formed during the prior night. Several types of commercial kits are available for determining peak LH, so women who find it difficult to determine a hormone change using one type can try another system or kit. Kits may vary in terms of sensitivity and variations may occur based on the dilution of the urine and hormonal conditions such as polycystic ovary syndrome (PCOS), which can give false positive tests. Basal body temperature (BBT) charts are not as precise for determining ovulation, with ovulation occurring over a span of several days of the thermogenic shift. In the last several years, multiple fertility apps have been launched, and a bracelet worn at night (Eva) has been advertised to provide information on a 5-day fertile window.

In some cases, women produce less than adequate amounts of vaginal lubricant. Various vaginal lubricants and chemicals, as well as saliva, used to improve coital satisfaction may interfere with sperm transport. Some men experience midcycle impotence because of the pressure of performing intercourse on demand. In

such cases the intercourse schedule should be less rigorous. The couple should also be told that among fertile couples, there is only approximately a 20% chance of conceiving in each ovulatory cycle, even with optimally timed coitus, and that it takes time to become pregnant; thus the terms *time* and *timing* should be emphasized during the initial counseling session. Couples should also be advised to cease smoking cigarettes and drinking caffeinated beverages in excess. Cigarette smoking and caffeine consumption have been shown independently in several studies to decrease the chances of conception. The common practice of vaginal douching also reduces the chance of conception by approximately 30%.

All couples should have a complete history taken, including a sexual history, and a physical examination, which is often ultrasound based. After this initial evaluation, tests should be undertaken to determine whether the woman is ovulating and has patent fallopian tubes and if a semen sample of the male partner is normal.

## Documentation of Ovulation

Preliminary information that the woman is ovulatory is provided by a history of regular menstrual cycles. If the woman has regular menstrual cycles, a serum progesterone level should be measured in the midluteal phase to provide indirect evidence of ovulation and normal luteal function. Although serum progesterone levels vary in the normal luteal phase in a pulsatile manner, a serum progesterone level greater than 3 to 5 ng/mL suggests some ovulatory function; however, it cannot indicate the adequacy of normal ovulation. **Progesterone levels of 10 ng/mL or higher** are found during at least 1 day of the luteal phase of normal ovulatory cycles in which conception occurred (Hull, 1982). Measurement of the daily BBT provides indirect evidence that ovulation has taken place but does not give precise information about ovulation timing as does the LH kit. The quality of ovulation cannot be determined accurately but may be suggested by a well-timed progesterone level. With the number of other methods such as phone apps and the bracelet, the use of the BBT, which is difficult for many women to do, has appropriately decreased.

Women with oligomenorrhea (menses at intervals of 35 days or longer) or amenorrhea who wish to conceive should be treated with agents that induce ovulation, regardless of whether they have occasional ovulatory cycles. Therefore for these women, direct or indirect measurement of progesterone is unnecessary until after therapy is initiated.

The endometrial biopsy is sometimes considered as a diagnostic method for the adequacy of ovulation and luteal function. ***We feel that an endometrial biopsy is not indicated in this setting of assessing ovulatory function***. It is invasive and painful, and it does not provide accurate information in terms of "endometrial dating" of the luteal phase, as was carried out in the past (Coutifaris, 2004); however, an endometrial biopsy may be indicated as a subsequent test when assessing for endometrial receptivity and ruling out chronic endometritis in the setting of repeated implantation failure or recurrent miscarriage, as will be discussed in other chapters.

## Semen Analysis

Although information about ovulation is being obtained, the male partner's reproductive system should be evaluated by means of a semen analysis. Most urologists dealing with male fertility issues require obtaining two semen analyses. Abnormalities in the semen analysis (male factor) **occurs in approximately 20% of couples with infertility as the sole factor and may be involved in 30% to 40% of cases overall**. The male partner should be advised to abstain from ejaculation for 2 to 3 days before collection of the semen sample. It is best to collect the specimen in a clean (not necessarily sterile) wide-mouthed jar after masturbation. It is important that the entire specimen be collected because the initial fraction contains the greatest density of sperm. Ideally, **collection should take place in the location where the analysis will be performed.** The degree of sperm motility should be determined as soon as possible after liquefaction, which usually occurs 15 to 20 minutes after ejaculation. Sperm motility begins to decline 2 hours after ejaculation, and it is best to examine the specimen within this period. Semen should not be exposed to marked changes in temperature and, if collected at home during cold weather, the specimen should be kept warm during transport to the laboratory.

Parameters used to evaluate the semen include volume, viscosity, sperm density, sperm morphology, and sperm motility. The last parameter should be evaluated in terms of percentage of total motile sperm and quality of motility (rapidity of movement and amount of progressive motility). Sperm morphology is an extremely important parameter and is correlated to fertilizing ability. Using strict criteria (Kruger), only approximately 4% or more of the sperm in an ejaculate may be considered normal according to the WHO criteria (Cooper, 2010). It should be remembered that the sperm analysis is a subjective test and that there is a fair degree of variability from test to test in the same man. Also, the semen profile reflects sperm production that occurred 3 months earlier, which is important to note if there was illness at that time. Table 40.4 lists the parameters that are generally considered normal for a semen analysis, according to the WHO study. It is beyond our scope here to discuss fully the causes and diagnostic evaluation of semen abnormalities. In broad terms, the various causes of semen abnormalities are cited in Table 40.5.

When semen analyses were performed on a group of men whose wives had conceived within the past 4 months, approximately 75% had at least one abnormal characteristic and 25% had two abnormalities. These results confirm that **there is normally a wide variability in the parameters used to characterize semen**. Because the characteristics of semen may vary over time and undergo normal biologic variability, it is best to repeat the test at least once if an abnormality is found. If abnormalities persist, **the male partner should have a urologic examination**. It is important not to miss a rare abnormality, such as a testicular tumor; in addition it has been appreciated that **male factor infertility is associated with other medical conditions** and subsequent problems (Eisenberg, 2015).

The comprehensive evaluation should include a history of physical examination (occasionally with ultrasound); hormonal evaluation (LH, follicle-stimulating hormone [FSH], testosterone, estradiol, prolactin [PRL], and thyroid-stimulating hormone [TSH]); and genetic abnormalities (karyotype and defects such as cystic fibrosis mutations and Y-chromosome microdeletions), particularly with severe sperm abnormalities (Practice Committee ASRM, 2012a).

**TABLE 40.4** Lower Fifth Percentile Values in Fertile Men*

| Parameter | Value |
|---|---|
| Semen volume (mL) | 1.5 |
| Sperm concentration (million/mL) | 15 |
| Total number (million/ejaculate) | 39 |
| Total motility (%) | 40 |
| Progressive motility (%) | 32 |
| Normal forms (%) | 4 |

Modified from Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update.* 2010;16(3):231-245.
*With time to pregnancy 12 months or less.

**TABLE 40.5** Causes of Semen Abnormalities

| Finding | Cause |
|---|---|
| **ABNORMAL COUNT** | |
| Azoospermia | Klinefelter's syndrome or other genetic disorder<br>Sertoli-cell–only syndrome<br>Seminiferous tubule or Leydig cell failure<br>Hypogonadotropic hypogonadism<br>Ductal obstruction, including Young syndrome<br>Varicocele<br>Exogenous factors |
| Oligozoospermia | Genetic disorder<br>Endocrinopathies, including androgen receptor defects<br>Varicocele and other anatomic disorders<br>Maturation arrest<br>Hypospermatogenesis<br>Exogenous factors |
| **ABNORMAL VOLUME** | |
| No ejaculate | Ductal obstruction<br>Retrograde ejaculation<br>Ejaculatory failure<br>Hypogonadism |
| Low volume | Obstruction of ejaculatory ducts<br>Absence of seminal vesicles and vas deferens<br>Partial retrograde ejaculation<br>Infection |
| High volume | Unknown factors |
| Abnormal motility | Immunologic factors<br>Infection<br>Varicocele<br>Defects in sperm structure<br>Metabolic or anatomic abnormalities of sperm<br>Poor liquefaction of semen |
| Abnormal viscosity | Cause unknown |
| Abnormal morphology | Varicocele<br>Stress<br>Infection<br>Exogenous factors<br>Unknown factors |
| Extraneous cells | Infection or inflammation<br>Shedding of immature sperm |

From Bernstein GS, Siegel MS. Male factor in infertility. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology.* 3rd ed. Cambridge, MA: Blackwell Scientific; 1991:629.

## Evaluation and Laboratory Tests

Aspects of the woman's medical history that should be highlighted include the following: any pregnancy complications if previously pregnant; previous pelvic surgery of any type; significant dysmenorrhea; dyspareunia or sexual dysfunction; abnormal cervical cytologic test results or procedures to treat cervical abnormalities; and use of medication, drugs, and tobacco. Family history should be explored for genetically related illnesses, birth defects, and, most importantly, the history of age of menopause in female family members. Finally, any symptoms suggestive of endocrine disorders should be solicited (e.g., weight changes, skin changes).

The physical examination should focus on extremes of body mass, skin changes, thyroid abnormalities, breast secretion, abnormal pain on abdominal or pelvic examination, and assessment of the vagina and cervix. In addition, if available, vaginal ultrasound performed at the same time may be extremely valuable in picking up abnormalities of the uterus (e.g., fibroids) endometrial thickness, pelvic masses, and ovarian morphology (e.g., polycystic appearance, unusually small). These may provide a guide for further testing.

In a healthy woman, a complete blood cell count (CBC), blood type, Rh factor, and rubella status are needed, together with the record of a Papanicolaou (Pap) test obtained within 3 years. Increasingly it is recommended (although not mandatory) to screen for genetic carrier status. Comprehensive screening for carrier status, including fragile X and other abnormalities such as cystic fibrosis, is easily carried out at the time of routine blood testing. Several laboratories can do such screening. Infectious disease screening (for chlamydia and gonorrhea) is carried out routinely in most practices at the time of the Pap test. Further infectious disease screening (e.g., syphilis, human immunodeficiency virus [HIV], hepatitis) is warranted, particularly for couples undergoing insemination or IVF.

In most women, and particularly in women older than 35 years, serum FSH and estradiol ($E_2$) levels should be obtained on cycle day 2 or 3. Elevated FSH values (>10 mIU/mL) suggest decreased ovarian reserve, which reflects the pool of viable oocytes remaining in the ovary. Levels greater than 20 mIU/mL afford a particularly poor prognosis; however, although FSH levels tend to fluctuate from cycle to cycle, once the FSH level has been elevated in a given cycle, the overall prognosis is reduced. $E_2$ levels, if elevated on days 2 and 3 (>70 pg/mL), do not allow for a valid interpretation of FSH values and may independently suggest a decreased prognosis regarding ovarian reserve.

**Antimüllerian hormone (AMH) has become a valuable standard for assessing ovarian reserve.** AMH, which is produced by the granulosa cells of small growing follicles, physiologically suppresses FSH stimulation of sustained follicular growth. Levels are highest in young women and lower with reproductive aging; various nomograms by age have been established (Seifer, 2011) (Fig. 40.4). Serum AMH decreases with aging, and when levels reach 0.05 ng/mL (essentially undetectable levels), menopause occurs within 4 to 5 years. Levels are higher in women with PCOS (Iliodromiti, 2013). The biggest concern with measurement of AMH is differences between assays because there is no international standard; however, in general, higher levels (>2 ng/mL) suggest a larger cohort of small available follicles and low levels (<0.5 ng/mL) suggest a decreased ovarian reserve. Values are of concern if they are less than 1 ng/mL. The level of AMH also reflects the sensitivity of the ovary to gonadotropic stimulation, and thus the choice of treatment when ovarian stimulation is desired. Unlike FSH, AMH values are fairly constant and stable throughout the menstrual cycle, particularly in the low ranges. Higher values, however, exhibit more variability in the early to midfollicular phase. It is now established that use of oral contraceptive pills decreases values by 15% to 20%.

### Use of Ultrasound in the Diagnostic Evaluation

It is most common to carry out a pelvic ultrasound evaluation as part of the investigation. By so doing, significant pathologic conditions such as fibroids, endometriosis, and other changes can be uncovered. In addition polycystic ovaries, which are prevalent, can be appreciated; and finally an **antral follicle count (AFC) can be obtained**, which is similar in value to the measurement of AMH, in the assessment of ovarian reserve. An age-related nomogram for AFCs has also been reported (Almog, 2011) (Fig. 40.5). For standardization it has been suggested that the AFC be obtained on cycle days 2 to 4, although an AFC can be obtained at other times in the cycle as long as all follicular structures over 10 mm are not counted.

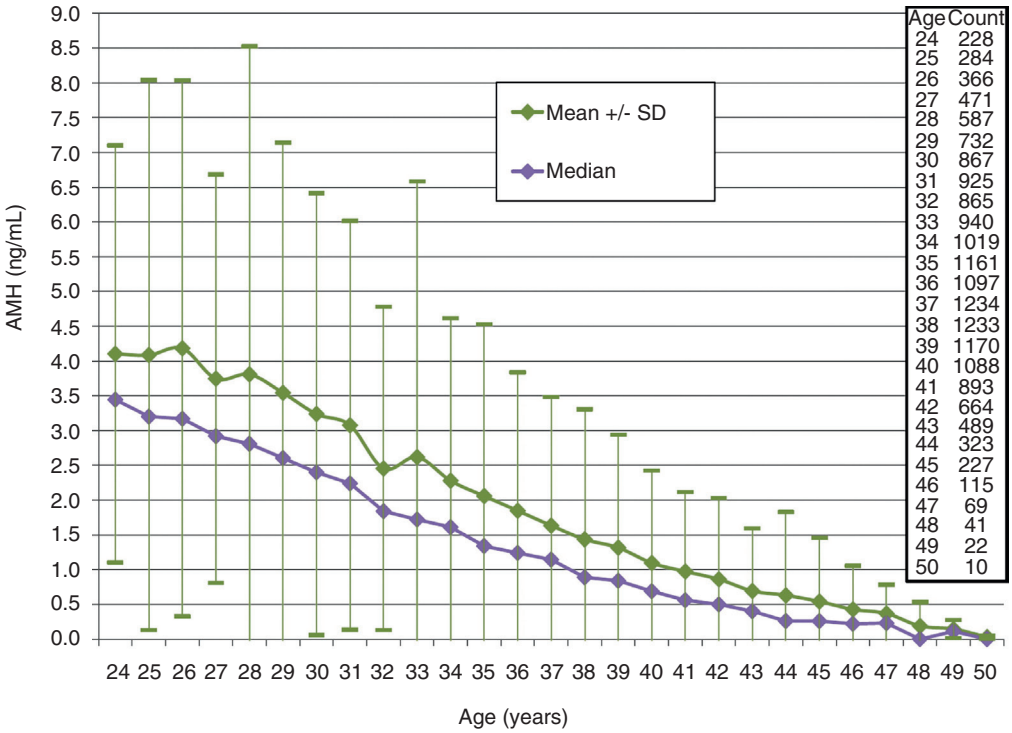



**Fig. 40.4** Antimüllerian hormone (AMH) age-specific median values with mean ± standard deviation values for women ages 24 to 50, n = 17,120, obtained at 1-year intervals. Note values are from a single laboratory using reagents from the older Beckman/Diagnostic Systems Laboratories (DSL) generation 1 assay; thus assays systems will vary for the absolute numbers but not for the trend of declining values with age. *SD,* Standard deviation. (From Seifer D, Baker VL, Leader B. Age specific serum AMH values for 17120 women presenting to fertility centers within the United States. *Fertil Steril.* 2011;95(2):747-750.)

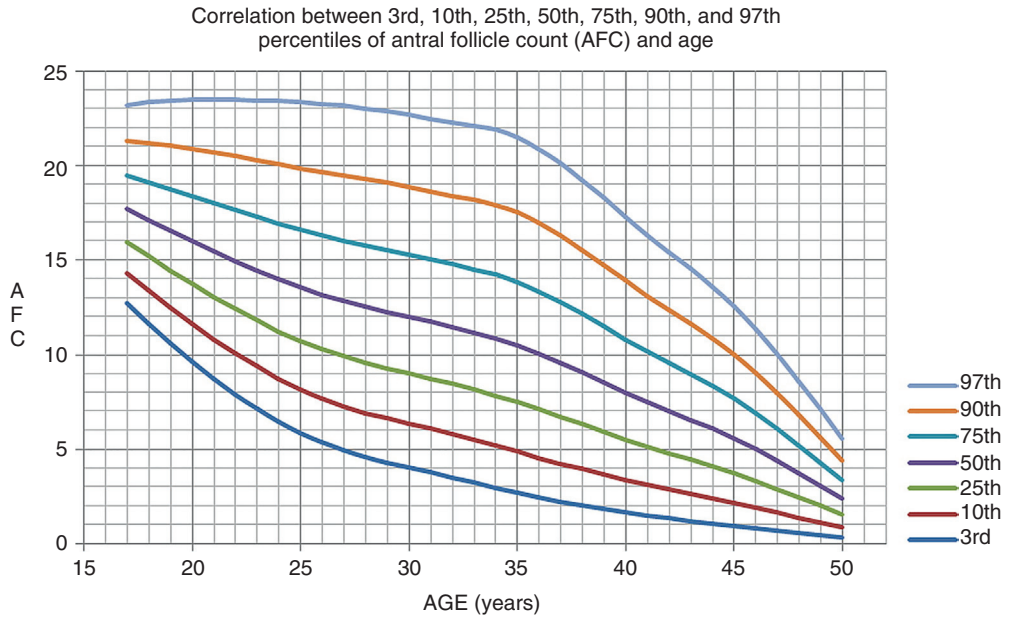



**Fig. 40.5** Age-related nomogram for antral follicle count depicted by various percentiles showing a biphasic decline and with a poor antral follicle count defined by a value under eight. (From Almog B, Shehata F, Shalom-Paz E, et al. Age-related nomogram for antral follicle count: McGill reference guide. *Fertil Steril.* 2011; 95(2):663-666.)

## Other Blood Testing

Some specialists obtain antibody titers for *Chlamydia trachomatis*, which if elevated may signify the possibility of tubal disease. It has been suggested that if the immunoglobulin G (IgG) antibody titer is greater than 1:32, 35% of patients have evidence of tubal damage. Whether this type of evaluation is routinely warranted as a focus for the infertility investigation continues to be debated.

Although not proven to be of major benefit in normal ovulatory women, most clinicians will measure TSH and PRL at the screening visit. TSH values in the normal range (<4.4 μU/mL), but higher than 2.5 mIU/mL are often considered to be abnormal in women presenting with infertility. This is because normal values in the first trimester of pregnancy should be less than 2.5 μU/mL; however, there is no evidence that values between 2.5 to 4 μU/mL affect fertility status or outcomes of pregnancy (Practice Committee ASRM, 2015). It is common to have slightly elevated PRL levels at the initial visit, which normalize when retested in the fasting state.

If an abnormality is found in one of the first two noninvasive diagnostic procedures (documentation of ovulation and semen analysis), it should be treated before proceeding with the more costly and invasive procedures, unless there is a history or findings suggestive of tubal disease. For example, if the woman has oligomenorrhea and does not ovulate each month, after a normal semen analysis is observed, ovulation should be induced with clomiphene citrate for two to three cycles before performing the other diagnostic measures. Provided that no other infertility factors are present, most anovulatory women (80%) conceive after induction of ovulation with therapeutic agents, and half the couples will conceive during the first three ovulatory cycles (Gysler, 1982).

If these initial diagnostic tests are normal, the more uncomfortable and costly hysterosalpingography (HSG) should be performed in the follicular phase of the next cycle.

## Hysterosalpingography

It is best to schedule the HSG during the week after the end of menses to avoid a possible pregnancy and also get better definition of the uterine cavity when the endometrium is still thin. The HSG should be avoided if there has been a history of salpingitis in the recent past or if there is tenderness on pelvic examination. As noted, most practices routinely screen for chlamydia and gonorrhea during the initial examination; however, we routinely prescribe prophylactic antibiotics at the time of HSG: doxycycline (100 mg twice daily for 3 days, starting 1 day before the procedure), but this recommendation is not universally followed. If a hydrosalpinx is seen with HSG, doxycycline should be continued for 1 week. The examination should be performed with use of a water-soluble contrast medium and image-intensified fluoroscopy. A water-soluble contrast medium enables better visualization of the tubal mucosal folds and vaginal markings than an oil-based medium. It is important to be able to evaluate the appearance of the intratubal architecture to determine the extent of damage to the tube (Fig. 40.6, *A* and *B*). Although it has

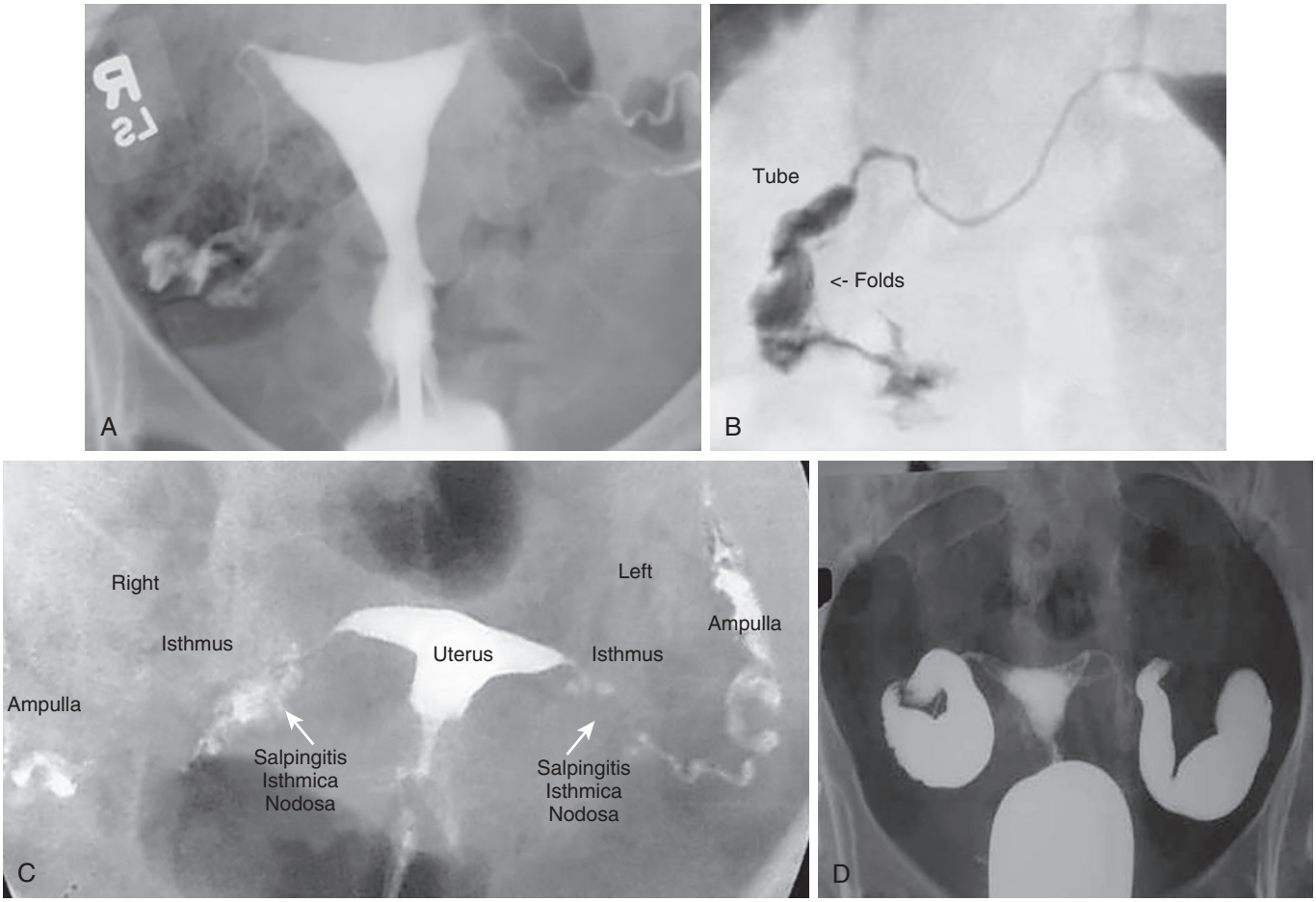



**Fig. 40.6** Representative hysterosalpingograms showing **(A)** a normal study, **(B)** normal ampullary folds, **(C)** bilateral salpingitis isthmica nodosa (proximal disease), and **(D)** bilateral hydrosalpinges (distal disease).

been debated for several years, **a large randomized trial in the Netherlands concluded that an oil-based contrast resulted in a higher ongoing pregnancy rate and live birth rate compared with water-based contrast** (Dreyer, 2017). An approach that has been advocated is to perform the test with a water-based medium, but to carry out tubal flushing with an oil base at the time of the procedure. It has been shown than flushing with oil contrast improves clinical pregnancy rates (Wang, 2019).

The diagnostic HSG provides important information about the magnitude of the disease process, if present, and provides information about the uterine cavity that cannot be obtained by laparoscopic visualization. The procedure can also determine whether salpingitis isthmica nodosa is present in the interstitial portion of the oviduct (Fig. 40.6, *C*). When an HSG shows lack of patency in one tube, this has been shown to be falsely positive, approximately 50% of the time at laparoscopy. Therefore it is not necessary to perform tubal reconstructive surgery on a woman with one patent tube. The finding of a normal endometrial cavity at the time of HSG obviates the need for hysteroscopy. If severe tubal disease, such as a large hydrosalpinx, is found at the time of HSG (Fig. 40.6, *D*), based on success rates, it is preferable for the couple to undergo IVF–embryo transfer (ET) than for the woman to have tubal surgery. If the hydrosalpinx is large and clearly visible on ultrasound, it is preferable to perform laparoscopic salpingectomy before IVF-ET because the pregnancy rate with IVF-ET may be decreased by as much as 40% (Zeyneloglu, 1998).

Quite often one or both tubes may show proximal obstruction. This may be the result of uterine spasm (contractions) caused by the discomfort of the procedure, or because of true obstruction; the latter may be only a mild obstruction caused by tubal debris. It has become common to attempt fluoroscopic-controlled selective cannulation of the proximal tube, either immediately or at a subsequent visit (Thurmond, 2008) (Fig. 40.7). This can be successful in up to 90% of cases, and if successful, it alleviates either unnecessary concern or the need for laparoscopy or IVF.

When the extent of tubal disease is unclear or the couple prefers not to undergo IVF-ET, diagnostic laparoscopy should be carried out in the follicular phase of the cycle. In general, the goal should be to have all tubal reconstruction carried out laparoscopically (discussed later).

## Postcoital Test (No Longer Routine)

Although important from a physiologic standpoint (cervical mucus being important for sperm transport), **the postcoital test (PCT) is now rarely indicated as a necessary part of the infertility investigation.** It is a very subjective test. A normal PCT is one in which at least five motile sperm are visible in normal cervical mucus obtained from the upper canal just before ovulation. A suboptimal test can be the result of technique, timing of the test, and problems with cervical mucus or with sperm. Although a good PCT has been correlated with a better prognosis for pregnancy, sperm have been recovered at laparoscopy when there was a poor PCT. Moreover, because the suggested treatment for a poor PCT is intrauterine insemination after ovarian stimulation, this is the exact next step taken, even if the PCT is normal, in the setting of unexplained infertility. Occasionally, as may happen with an orthodox Jewish couple, a semen analysis cannot be obtained. Here, a PCT provides a surrogate for visualizing motile, normal-appearing sperm.

## Laparoscopy: Is It a Routine Part of the Investigation?

In the past, this was an obligatory final step in the infertility investigation when all other test results were normal. Data have shown that in 20% to 40% of cases, some minor abnormalities may be found (e.g., endometriosis, adhesions), which may have a bearing on fecundability. Obviously, if there is something suspicious on ultrasound or examination, there has been prior pelvic surgery or appendicitis, or there is pelvic pain or dyspareunia, the index of suspicion is increased. The probability that peritubal adhesions of sufficient severity to cause infertility will be found at the time of laparoscopy is less than 5% in a woman with no history of salpingitis or symptoms of dysmenorrhea, a normal bimanual pelvic examination, and normal antibody titers (if obtained) (Fatum, 2002). Provided the woman is younger than

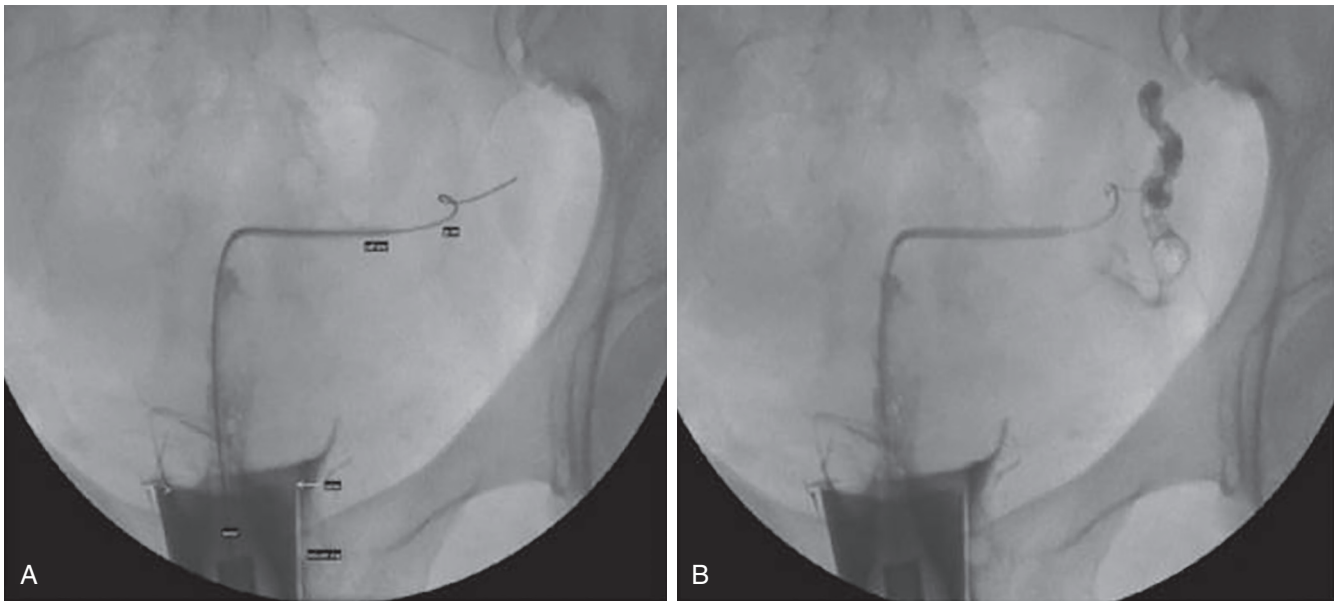



**Fig. 40.7** Technique of tubal cannulation using a vacuum cup on the cervix. **A,** Introduction of a 5.5-French catheter into the tubal ostium under fluoroscopy, by a 0.015-inch guidewire into the fallopian tube for dislodgement of debris. **B,** Injection of contrast through a 3-French catheter into the tube confirming successful cannulation and a normal-appearing patent tube. (From Thurmond AS. Fallopian tube catheterization. *Semin Intervent Radiol.* 2008;25(4):425-431.)

40 years and is having ovulatory cycles, and there is an acceptable semen analysis and an age-appropriate maker of ovarian reserve such as AMH, **several cycles of COS and intrauterine insemination may be undertaken before performing diagnostic laparoscopy or going directly to IVF-ET**. At this juncture, a decision can be revisited about whether performing a laparoscopy should be considered, although many couples usually prefer to proceed with IVF-ET, particularly if they have insurance coverage for IVF.

## Additional Testing for Couples Presenting With Infertility

### Significance of a Diagnosis of Luteal Deficiency (Is This a True Diagnosis?)

Although suggested for many years, it has never been established that luteal phase defects cause infertility. This pertains to women who are completely normal on evaluation and have regular cycles. Women who are oligoovulatory and have longer cycles and women with elevated PRL levels can have luteal inadequacy that is corrected by lowering of PRL levels and/or ovulation induction.

The diagnosis of luteal deficiency used to be made on finding serum progesterone levels consistently less than 10 ng/mL 1 week before menses or finding consistent evidence for a histologic delay (>3 days) in the pattern of the normal secretory endometrium, indicating an inadequate effect of progesterone on the endometrium. This endometrial defect had to be found in two consecutive cycles. Erroneous diagnoses of this entity occur because of cycle variability and the subjective interpretation of histologic dating criteria. There is at least a 10% disagreement of more than 2 days when the same observer dated the specimens on two separate occasions, and even more interobserver variability. As noted earlier, studies have confirmed the lack of efficacy of the endometrial biopsy (Coutifaris, 2004). ***Routine endometrial biopsies for the diagnosis of infertility should not be carried out.***

As noted regarding the PCT, ovarian stimulation with intrauterine insemination (IUI) is often the first empirical treatment for unexplained infertility. This essentially treats the luteal inadequacy, if it exists, preempting the need for invasive and imprecise endometrial biopsies.

### Immunologic Factors in Subfertility

Substantial evidence from animal studies has indicated that antibodies can be induced in females from antigens obtained from organs in the male reproductive tract and that these antibodies interfere with normal reproduction. Both sperm-agglutinating and sperm-immobilizing antibodies have been found in the serum of some infertile women, but also in the serum of fertile control subjects. Agglutinating antibodies are found more often than immobilizing antibodies in most series, and, in some reports, the incidence of sperm-agglutinating antibodies in infertile women is similar to that in the control group. Even with the finding of sperm agglutination or immobilization in interactions with serum (in vitro), it has not been demonstrated that a similar degree of sperm inactivation occurs in the lower genital tract. Thus there is **no definitive evidence that sperm agglutination or immobilization in the serum of infertile women is the cause of their infertility**. One of the reasons for this discrepancy is that both serum assays measure mainly immunoglobulin M (IgM) and IgG antibodies, whereas the antibodies locally produced in the genital tract are mainly IgA. Thus some investigators have measured antisperm antibodies in cervical mucus and found a correlation between their presence and infertility; however, no data have shown that the finding of antibodies against sperm in the male or female partner is a cause of infertility. In addition, corticosteroid treatment of the male or female partner does not significantly increase the pregnancy rate compared with no therapy.

Autoimmunity to sperm in semen and serum has been found in some infertile men, particularly those who have had testicular infection, injury, or a surgical procedure such as vasectomy reversal. Men with these antibodies have been treated with corticosteroid therapy and sperm-washing techniques. Nevertheless, the effectiveness of such treatment remains to be established.

Four prospective studies have reported the incidence of fertility occurring after a diagnostic infertility evaluation was performed in which the presence of antisperm antibodies was documented (Collins, 1993). These studies were performed in four different laboratories in three different countries. Several different techniques were used for the antibody tests. All four studies showed **no correlation between the presence of antisperm antibodies in either member of the couple and the chance of conception**. Pregnancy rates over time were similar in couples who had or did not have antisperm antibodies. Therefore tests to detect these antibodies as part of the diagnostic infertility evaluation are not justified because their presence does not affect fecundity.

### Significance of Infectious Diseases in Subfertility

Some researchers have suggested that asymptomatic, or occult, infection of the upper female genital tract and male genital tract is a cause of infertility. As early as 1973, it was suggested that infection with what was then called *T-mycoplasma* in the male could interfere with normal sperm function, and infection of the female reproductive tract could interfere with normal sperm transport. The current name now used for these organisms is *Ureaplasma urealyticum*. Two other microorganisms found in the female genital tract are *Mycoplasma hominis* and *M. fermentans*. These organisms have been found to colonize in the lower genital tract of some women and not to cause any problems making this a difficult issue in terms of pathology. Although it has been reported that treatment of infertile couples with antibiotics, such as tetracycline or doxycycline, that eradicate these organisms, may result in high pregnancy rates, **controlled studies have reported no difference in pregnancy rates between couples treated with antibiotics and those not treated**. Harrison and colleagues have studied 88 infertile couples with no demonstrable cause of infertility. One-third were treated with doxycycline, one-third received placebo, and one-third received no treatment. T-mycoplasma was isolated from approximately two-thirds of the couples in each group and was eradicated only in the group treated with doxycycline. Nevertheless, conception rates were similar in each group (Harrison, 1975), as was also reported by Matthews and coworkers (Matthews, 1978) Other investigators have suggested that asymptomatic *Chlamydia trachomatis* infection may also cause infertility, but the dosage of doxycycline used in the randomized studies cited earlier would also have eradicated these organisms. Thus there is no evidence that asymptomatic infection of the genital tract of the human male or female causes infertility.

### Are Other Tests of Sperm Function Indicated?

In that the semen analysis is subjective and variable, it has long been suggested that other more functional tests would improve the evaluation of the male partner (Oehninger, 2014).The zona-free hamster egg penetration test originally described by Yanagimachi and associates was a test developed to predict the fertilizing ability of sperm and provides an additional, perhaps more sensitive, parameter for assessing sperm function than routine semen analysis; however, many variables factors affect the test results. It has been shown that this test does not correlate well with IVF of human eggs. The sensitivity and specificity of the hamster egg penetration assay (sperm penetration

assay) is considered to be too low to justify its routine use as part of the infertility investigation.

Some functional tests of sperm (such as the hypoosmotic swelling test) assess the integrity of the sperm cell membrane, and others (the zona pellucida binding test, acrosome reaction, and the hyaluronan binding assay) assess maturity and viability (Oehninger, 2014); however, there is **no evidence, at present, that these tests add information to the infertility investigation** or affects treatment. The **DNA fragmentation test** in sperm has become popular. This test, which is carried out by flow cytometry or direct microscopy, determines the rate of DNA fragments; a DNA fragmentation index of more than 30% has been suggested to indicate a poorer rate of fertilization and therefore suggests the need for IVF with intracytoplasmic sperm injection (ICSI); however, at present, **there is no evidence that this correlates with the success of IVF, and it cannot be advocated as a routine test** (Practice Committee ASRM, 2014).

## PROGNOSIS OF VARIOUS DIAGNOSES UNCOVERED BY THE INFERTILITY INVESTIGATION

Before discussing the specific treatments for abnormalities uncovered by the investigation, it is useful to frame a prognosis for the couple depending on what factor(s) have been found.

The highest probability of conception with treatment other than with IVF-ET occurs among couples in whom anovulation is the only abnormality, with substantially lower probabilities of pregnancy in couples with tubal disease and sperm abnormalities (Hull, 1985) (Fig. 40.8). Although these data are older, this information from Hull still provides the best available comparisons. Age is a major prognostic factor. Among a group of infertile couples with unexplained infertility who were followed for 2 years without treatment after the evaluation was completed, it was found that the chances of becoming pregnant were greater in women younger than 35 years (~75%) than in women older than 35 (50%) (Hull, 1985) (Fig. 40.9). The duration of infertility is also of prognostic significance. The cumulative conception rate at the end of 2 years without therapy for those couples was much greater for those who had tried to conceive for less than 3 years before evaluation (~75%) than those who had tried to conceive for more than 3 years (~30%) (Hull, 1994) (Fig. 40.10). In three of the four studies of infertile couples who received no therapy mentioned earlier, more than 50% of the couples who eventually conceived did so in the first year after completing the infertility evaluation.

In couples with no known factors, it has been suggested that couples have a better prognosis for spontaneous conception

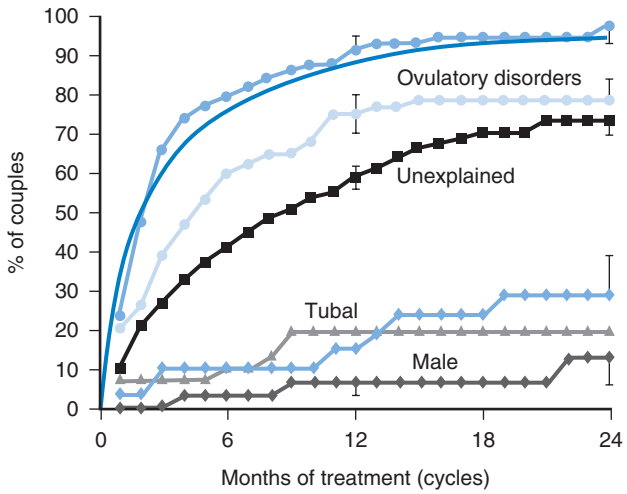



**Fig. 40.8** Effect of various treatments on fecundability: ovulatory, tubal, and male factors. (Modified from Hull MG, Glazener CM, Kelly NJ, et al. Population study of causes, treatment, and outcome of infertility. *Br Med J.* 1985;291(6510):1693-1697.)

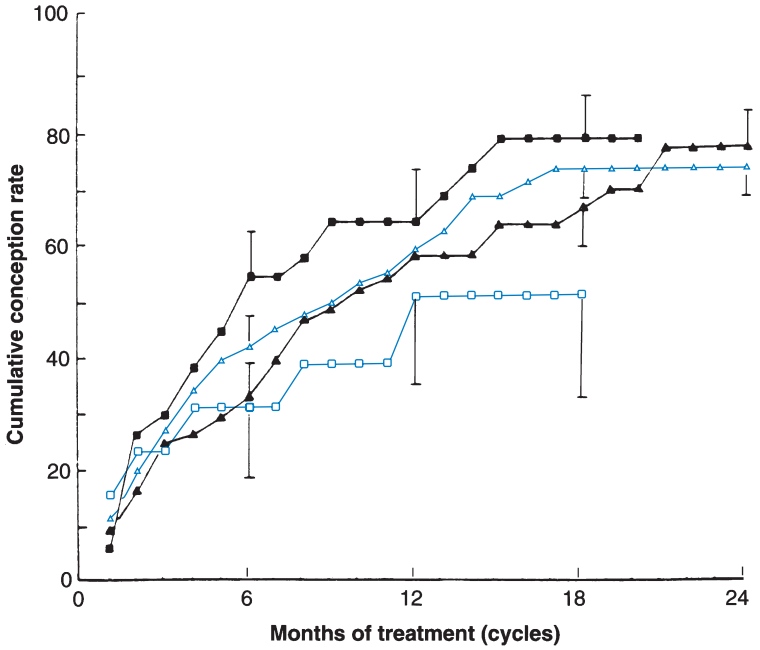



**Fig. 40.9** Cumulative rates of conception from first attendance at clinic in couples with unexplained infertility related to age of woman. Rates for each age group are shown: solid squares, younger than 25 years; blue triangles, 25 to 29 years; solid triangles, 30 to 34 years; blue squares, older than 35 years. Standard errors of proportions are given at 6, 12, 18, and 24 months. (From Hull MG, Glazener CM, Kelly NJ, et al. Population study of causes, treatment, and outcome of infertility. *Br Med J.* 1985;291(6510):1693-1697.)

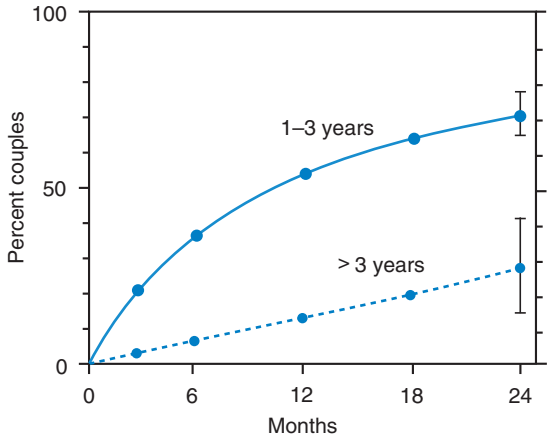



**Fig. 40.10** Cumulative pregnancy rates in unexplained infertility without treatment related to duration of infertility. (From Hull MG. Effectiveness of infertility treatments: choice and comparative analysis. *Int J Gynaecol Obstet.* 1994;47(2):99-108.)

based on their age and the time of trying to conceive. A prognostic score can be calculated (Hunault, 2004), and for those with a good prognosis, it has been suggested that these couples can just continue to try (**expectant management**) and it may not be necessary to start **empiric treatment** (discussed later). Generally, for couples presenting with the inability to conceive, even if no factors have been found (unexplained infertility), to increase their chances of conception or to shorten the time interval until conception takes place, various empiric treatments have been advocated. This generally increases the fecundity rate with unexplained infertility from a **baseline of around 4% to 9% to 10% per cycle,** as will be discussed later in the Unexplained Infertility section.

## TREATMENT OF VARIOUS CAUSES OF INFERTILITY

The management of the various causes of infertility will be presented here in the order generally followed in an infertility investigation.

### Medical Treatment for Anovulation and Subovulatory Function

At times it may be found that some women are oligoovulatory or may not have consistent normal ovulatory function based on cycle length and levels of progesterone. They should be treated as other women with anovulation as addressed here. Therapeutic agents currently available to induce ovulation are clomiphene citrate, letrozole, and urinary and recombinant gonadotropins. Adjunctive treatments include gonadotropin-releasing hormone (GnRH) agonist and antagonists, as well as human chorionic gonadotropin (HCG), which is used to trigger ovulation. In addition, as discussed in Chapter 39, if anovulation is caused by hyperprolactinemia, dopamine agonists are an effective means of inducing ovulation, although most women will also respond to clomiphene or letrozole. As noted in Chapter 38, ovulation may be induced by corticosteroid therapy in women with congenital adrenal hyperplasia, but here again in the adult-onset patient, clomiphene or letrozole can be used as well.

#### Clomiphene Citrate

Clomiphene citrate (CC) is the usual first-line pharmacologic agent for treating women with anovulation or subovulatory function as long as there is sufficient estrogen production. CC is a racemic mixture of en- and zu-clomiphene, which act as estrogen antagonists. The former has a shorter half-life and is more active than the zu-clomiphene isomer, which has a much longer half-life and is more estrogen agonistic than antagonistic. **CC acts by competing with endogenous circulating estrogens for estrogen receptor binding sites on the hypothalamus**, thereby blocking the negative feedback of endogenous estrogen. GnRH is then released in an enhanced manner, stimulating FSH and LH, which in turn cause oocyte maturation, with increased $E_2$ production. CC is usually given daily for 5 days, beginning 3 to 5 days after the onset of spontaneous menses or withdrawal bleeding induced with a progestogen.

During the days when CC is taken, serum levels of LH and FSH rise, accompanied by a steady increase in serum $E_2$ level. After CC is discontinued, $E_2$ levels continue to increase and the negative feedback on the hypothalamic-pituitary axis causes a decrease in FSH and LH levels, similar to the change seen in the late follicular phase of a normal ovulatory cycle. Approximately 5 to 9 days (mean, 7 days) after the last CC tablet, the exponentially rising level of $E_2$ from the dominant follicle has a positive feedback effect on the pituitary or hypothalamus, producing a surge in LH and FSH levels, which usually results in ovulation and luteinization of the follicle.

Timing of ovulation can be determined by using LH monitoring kits and serum progesterone can be measured 1 week after presumed ovulation. A rise in serum progesterone level greater than 3 ng/mL correlates well with the finding of a secretory endometrium, but it has been reported that the **maximal midluteal progesterone levels in CC-induced ovulatory conception cycles are consistently more than 15 ng/mL** (Hammond, 1983). These levels are higher than the 10 ng/mL level, which is the minimum concentration of progesterone found 7 days after ovulation in spontaneous ovulatory conception cycles (Hull, 1982). The level is higher with CC because more than one follicle usually matures and undergoes luteinization.

Various treatment regimens have been advocated for the use of CC. Most start with an initial dosage of 50 mg/day for 5 days, beginning on the third to fifth day of spontaneous or induced menses. If presumptive evidence of ovulation occurs with this dosage, the same dosage of CC is taken in subsequent cycles until conception occurs. If ovulation fails to occur with the initial dosage, a sequential, graduated, increasing dosage regimen has proven to be effective, with a minimum of side effects. With this regime, if ovulation does not occur with the 50-mg dose, the dosage of drug is increased in the next treatment cycle to 100 mg/day for 5 days. If ovulation does not occur with 100 mg/day in subsequent cycles, the dosage is sequentially increased to 150 mg. In the past we have used doses up to 250 mg, with and without HCG (Lobo, 1982). In the 10 years' experience with this treatment regimen as reported by Gysler and associates, approximately half of the women who ovulated and half of those who conceived did so after treatment with the 50-mg/day regimen, and an additional 20% ovulated with the 100-mg/day dosage (Gysler, 1982). Approximately 25% of all women who ovulated or conceived did so after treatment with a higher dosage regimen, indicating the value of the individualized sequential treatment regimen; however, from a practical standpoint, it is **unusual to use doses higher than 150 mg,** particularly when adjuncts are available, such as metformin in overweight women with PCOS or switching to letrozole. In the past, and still occasionally, dexamethasone has been used as an adjunct as well.

A newer regimen, the **stair-step regimen**, does not wait for menses after a failed response before moving to the next dose (Hurst, 2009); thus if there is no follicular development on ultrasound 5 days after the last clomiphene tablet, the patient is immediately placed on 100 mg for 5 days and subsequently to 150 mg for 5 days in the same cycle if follicular development does not occur. Although preliminary retrospective reports have shown that this is a reasonable approach to hasten therapy, prospective randomized trials are still in progress.

With the dosage regimen of CC up to 250 mg, more than 90% of women with oligomenorrhea and 66% with secondary amenorrhea and normal estrogen status will have presumptive evidence of ovulation. Although **only approximately 50% of patients who ovulate with this treatment will conceive,** (Gysler, 1982). The fecundability during several months of treatment with CC, if no other causes of infertility are present, are similar to those of a normal fertile population. Using life table analysis, the monthly pregnancy rate **(fecundability) of women treated with CC who had no other infertility factor was 22%** compared with a rate of 25% for women discontinuing diaphragm use. The monthly fecundability remained constant throughout almost 1 year of treatment. Almost all the anovulatory women without other infertility factors in this series, as well as other women with correctable infertility factors, had conceived after 10 cycles of treatment. This rate is also similar to the use of gonadotropins (Messinis, 1997) (Fig. 40.11).

These data indicate that discontinuation of therapy is the major reason for the reported difference in ovulation and conception rates in anovulatory women treated with CC; however, despite these data, many investigators believe that pregnancy rates are lower with CC than might be expected based on ovulation rates, and other factors (in some women), such as cervical mucus and endometrial problems, explain this discrepancy. In ovulatory women who respond to CC, **because as many as 80% of women will conceive by 3 months if there are no other factors,** additional testing should be done after 3 months if not carried out earlier. A HSG should be performed at this time. A semen analysis should be done before starting CC. When conception occurs after ovulation has been induced with CC, the incidence of multiple gestation is increased to approximately 8%, with almost all being twin gestations; however, when the drug is used in normally ovulating women with unexplained infertility, the rate increases to almost 20%. The incidence of **clinical spontaneous abortion ranges between 15% and 20%, similar to the rate in the general population**. The rates of intrauterine fetal death and congenital malformation are also not significantly increased. Animal data have shown that if the drug is given in high dosages during the time of embryogenesis, there is an increased incidence of fetal anomalies; however, limited human data have indicated that if the drug is ingested during the first 6 weeks after conception has occurred, the incidence of fetal malformation, although higher (5.1%) than in the normal non infertility population, it is not significantly increased. Women with infertility in general have been noted to have a higher anomaly rate, even when conceiving without medications. Although no definitive data have shown that the drug is teratogenic in humans, it is best that the woman be tested for pregnancy before each course of treatment.

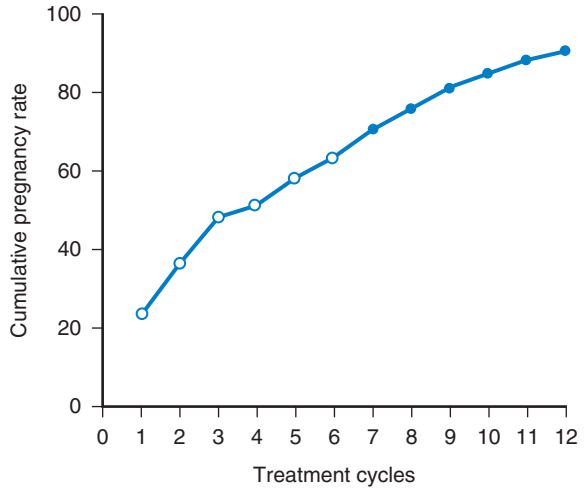



**Fig. 40.11** Cumulative pregnancy rate of 60% at 6 months with clomiphene. (From Messinis IE, Milingos SD. Current and future status of ovulation induction in polycystic ovary syndrome. *Hum Reprod Update.* 1997;3(3):235-253.)

Clinically palpable ovarian cysts occur in approximately 5% of women treated with CC but in less than 1% of treatment cycles. It is most efficient to carry out an ultrasound scan before prescribing CC, which is our current standard of practice. The cysts usually range in size from approximately 3 to 5 cm, do not require surgical excision, and usually regress spontaneously. On ultrasound smaller "cysts" are often encountered, but these should not preclude starting CC if they are less than 25 mm in diameter. Cysts can occur in any treatment cycle with any dosage, and the incidence is not increased with the higher dosages of drug. Recurrence of cyst formation with the same dosage is uncommon. Other side effects, which occur in less than 10% of women treated with CC, include vasomotor flushes, blurring of vision, abdominal pain or bloating, urticaria, and a slight degree of hair loss.

Up to 10% of women treated with CC fail to ovulate with the highest dosage. Older data have suggested that this so-called resistance is not caused by the inability of the hypothalamic-pituitary axis to respond, but to the lack of the ovarian response to raised gonadotropin levels. Contributors of **CC resistance include body mass index, free androgen, and insulin; higher values all contributing to this resistance**. Although various prediction models have been generated to determine the CC response, none has proven to be useful prospectively. Findings in women with PCOS also suggest that **higher levels of AMH may contribute to CC resistance** and affect the dosage required for gonadotropins in women with PCOS; AMH inhibits FSH action in the ovary (Mahran, 2013).

Some data suggest that in women with elevated levels of androgen, particularly dehydroepiandrosterone sulfate (DHEAS), the use of low doses of dexamethasone may enhance the ovulation-inducing effect of CC. This approach is less often used today. Other adjuncts that have been tested, but that lack validation, include adding a dopamine agonist such as bromocriptine and antiandrogens. Metformin and insulin sensitizers have also been used as adjunctive treatments.

## Metformin and Other Insulin Sensitizers

Metformin, a biguanide used to control blood sugar in diabetics, has a role in ovulation induction in women with PCOS and has been shown to be superior to placebo. Although not a true insulin sensitizer, it decreases hepatic glucose production and has some minor peripheral action, leading to some decrease in insulin resistance. It also has a direct role in inhibiting ovarian androgen steroidogenesis and acts on the endometrium.

Studies have confirmed the efficacy of metformin over placebo in inducing ovulation in women with PCOS; however, in direct comparisons with clomiphene, it was inferior to clomiphene in terms of live birth rates in women with PCOS (Legro, 2007) (Fig. 40.12). Therefore although not necessarily a first-line choice in women with PCOS, it is clearly an adjunct and may be helpful in women who exhibit some degree of insulin resistance; however, it should be considered as a preliminary option in heavy or obese women and for those with impaired glucose tolerance or significant insulin resistance before ovulation induction with other agents.

The typical dosage of metformin is 1500 mg/day. It is preferable to use long-acting tablets (extended release or extra strength) available in 500- and 750-mg tablets and to ingest them all at the same time during a meal, preferably at dinner; however, it should be initiated only at 500 mg and titrated up over several weeks. This is because of gastrointestinal effects (e.g., nausea, vomiting,

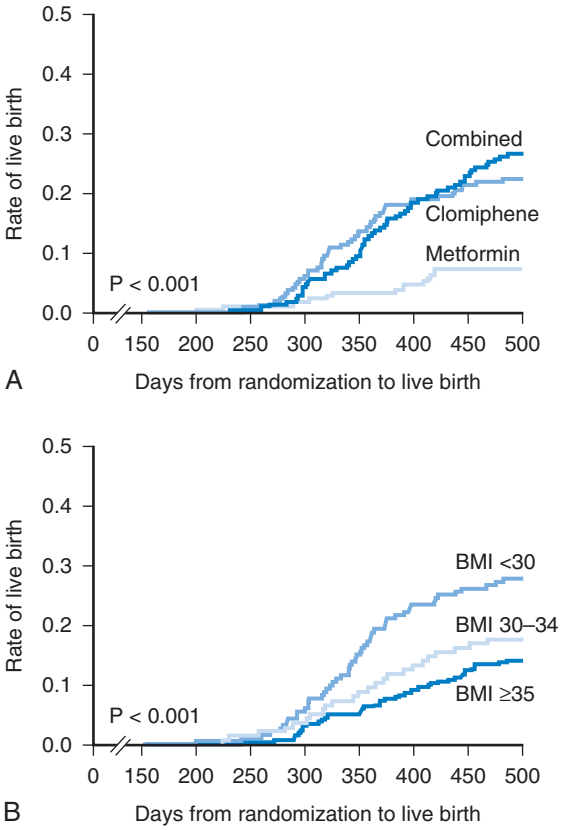



**Fig. 40.12** Kaplan-Meier curves for live birth, according to study group. **A,** All three groups. **B,** Groups divided by body mass index (BMI). (From Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med. 2007;*356(6):551-566.)

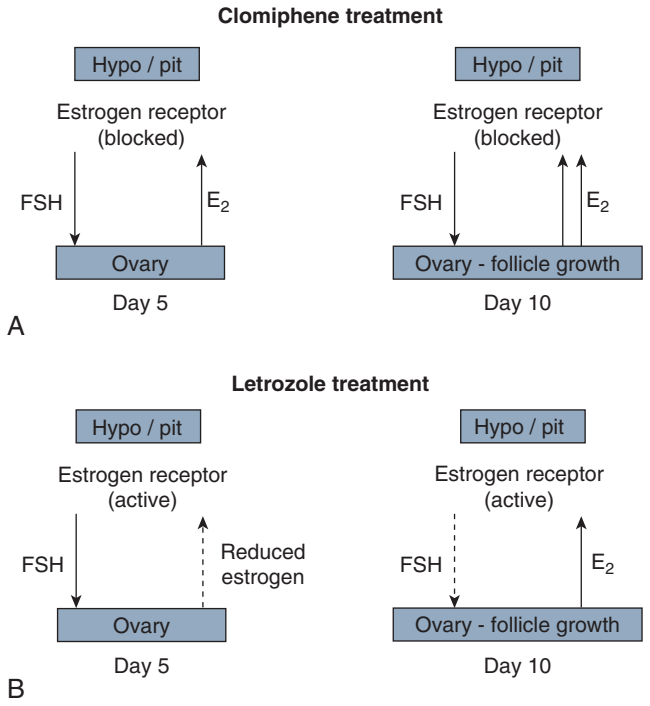



**Fig. 40.13** Clomiphene citrate **(A)** and letrozole treatment **(B).** $E_2$, Estradiol; *FSH,* follicle-stimulating hormone; Hypo/pit, hypothalamic-pituitary axis. (From Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. *J Clin Endocrinol Metab.* 2006;91(3): 760-771.)

and diarrhea), which are the primary concern with metformin and preclude its use in up to 20% of women.

Lactic acidosis is a rare complication that occurs primarily in older individuals; however, checking chemistry blood levels after 3 months of metformin is good practice, and women also should be reminded not to drink alcohol heavily, although the occasional drink is acceptable. Minor elevations in liver enzymes, which often are caused by "fatty liver," are not a contraindication to using metformin. Many endocrinologists advocate a dose of 2000 mg/day for heavier women.

When metformin alone is prescribed for anovulatory women who wish to conceive, the ovulation rate is approximately 60% in adherent women. In CC-resistant patients, those who fail to ovulate with 150 mg/day (although the data are mixed), approximately 25% of women will respond to CC with metformin. Metformin is a category B substance for pregnancy and has been continued through the first trimester and beyond in some patients.

## Letrozole

**Aromatase inhibitors are efficacious as primary agents for ovulation induction**. Most of the experience is with letrozole. The mechanism of action is inhibition of $E_2$ production during the 5 days of administration, which results in negative feedback and an increase in FSH levels, much like the response to CC. Intraovarian androgen levels are also increased, which may enhance FSH sensitivity. Letrozole (2.5 or 5 mg) per day for 5 days is administered for 5 days, beginning on cycle days 3 to 5.

Because **letrozole is short acting**, the problems of thick cervical mucus or a thin endometrium associated with CC have not been reported with letrozole; however, $E_2$ levels are usually lower at ovulation. Pregnancy rates are comparable to those with CC alone, and there has been a suggestion for a reduced incidence of multiple pregnancies because of its shorter half-life and lack of stimulation of gonadotropins beyond the early follicular phase (Casper, 2006) (Fig. 40.13). A randomized trial comparing letrozole and CC in **women with PCOS showed the superiority of letrozole in terms of live births** (Legro, 2014) (Fig. 40.14). In this trial there were no differences in adverse effects or congenital anomalies, and the multiple pregnancy rates were comparable, which is at odds with the purported theoretical advantage of letrozole over CC. Including this trial, a meta-analysis from Cochrane also confirmed the superiority of letrozole (Franik, 2014). In that it has also been deemed to be cost effective, letrozole should be considered the first-line treatment (over CC) in women with PCOS, although to date it still has not been approved by the U.S. Food and Drug Administration (FDA) for ovulation induction; however, there is **no evidence of the superiority of letrozole over CC in women without PCOS**; indeed, CC performed better when used to enhance ovulation in women with unexplained infertility (discussed later).

There is little information about the effects of letrozole in CC-resistant patients, but anecdotally it has been found to be effective in this regard in many women. Letrozole with gonadotropins has also been used for ovarian stimulation. It has been suggested that it can reduce the gonadotropin dose needed when used as a sequential regimen (letrozole priming followed by gonadotropins), and it may be used in combination with gonadotropins in poor responders for IVF.

## Gonadotropins

Gonadotropin therapy is indicated for ovulation induction when estrogen levels are low and when there is no repose to CC or

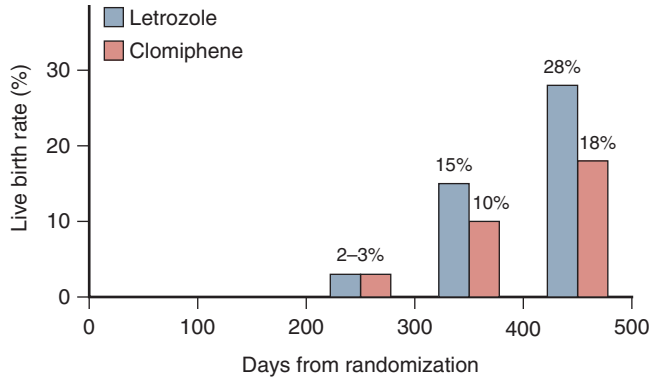



**Fig. 40.14** Live birth rates in a randomized trial of letrozole versus clomiphene in women with polycystic ovary syndrome. (Data from Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med.* 2014;371(2):119-129.)

letrozole. Low serum $E_2$ levels (usually less than 20 to 30 pg/mL) or lack of withdrawal bleeding after progestogen administration signifies a state that will be unresponsive to oral therapies (CC, letrozole) that are dependent on a negative feedback system. Apart from this indication in usually amenorrheic women, it is appropriate to use gonadotropins when there is resistance to CC or letrozole. Gonadotropins have also been used when there has been the inability to conceive after several (four to six) cycles of CC or letrozole, although this indication is not as commonly applied today.

The original gonadotropin preparations were extracts of postmenopausal urine. Although purified, they contained large amounts of protein contaminants. These preparations are used less often today but are still available worldwide (Pergonal, Humegon). Newer preparations with additional purification have allowed them to be administered subcutaneously (SC) rather than intramuscularly (IM). These preparations (such as Menopur) are titrated to provide an equal quantity of LH (75 IU) and FSH (75 IU) in one ampule.

Further modifications of these urinary products have eliminated most of the LH activity and provided a relatively pure FSH urinary preparation (urofollitropin for injection [Bravelle or Metrodin], containing 75 IU FSH/ampule). All nonrecombinant preparations, because they are extracted from human sources, have batch to batch variability in terms of biologic activity.

Recombinant pure FSH preparations (from Chinese hamster ovarian cells) are currently available for subcutaneous administration (Gonal-F, Follistim, 75 IU FSH). Recombinant pure LH has also become available as a supplement (Luveris, 75 IU LH), although it is unclear if the addition of LH is really necessary in most cases.

Because each woman responds individually to the dosage of gonadotropins, even the same woman in different treatment cycles, it is essential to monitor treatment carefully with frequent measurements of estrogen levels and ovarian ultrasonography. **Close monitoring (ultrasound and $E_2$) is important to assess the adequacy of the response and to avoid ovarian hyperstimulation.**

There is a different concept regarding induction of ovulation with gonadotropins when the problem is anovulation or when gonadotropins are used in the setting of unexplained infertility or for the purposes of IVF (discussed later). Many practitioners often lose this concept, which then leads to a high rate of hyperstimulation and multiple pregnancies. It is for these reasons that gonadotropins are often avoided in the setting of failure to conceive after several ovulatory cycles of CC or letrozole, favoring an approach of going directly to IVF.

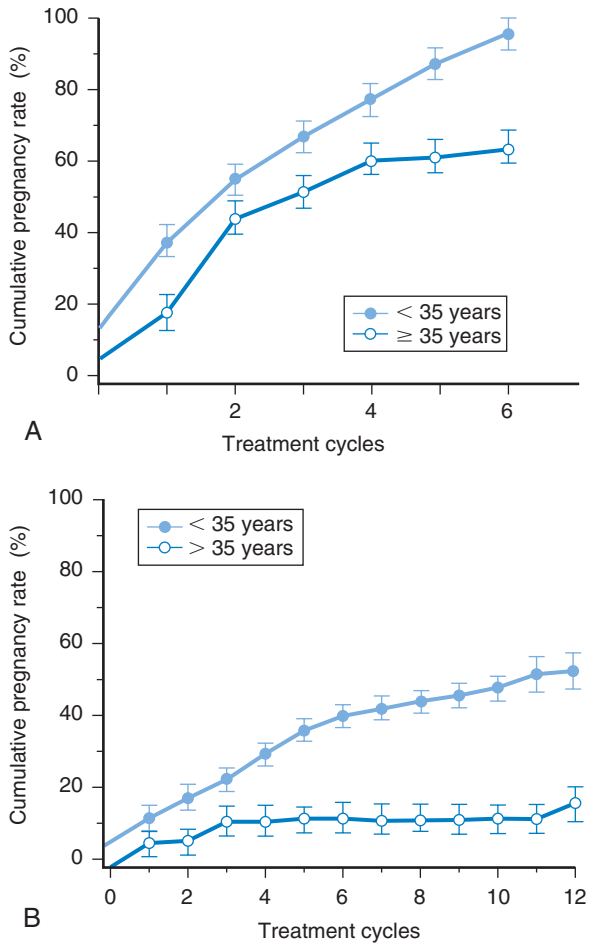



**Fig. 40.15 A,** Cumulative pregnancy rates for hypogonadotropic anovulatory women (World Health Organization [WHO] group I) treated with gonadotropins. *Solid circles* represent the cumulative pregnancy rate in women younger than 35 years. *Open circles* represent the cumulative pregnancy rate in women older than 35 years. **B,** Cumulative pregnancy rates after gonadotropin treatment for anovulatory women who did not respond to clomiphene induction of ovulation (WHO group II). *Solid circles* represent the cumulative pregnancy rate in women younger than 35 years. *Open circles* represent the cumulative pregnancy rate in women older than 35 years. (From Lunenfeld B, Insler V. Human gonadotropins. In: Wallach EE, Zacur HA, eds. *Reproductive Medicine and Surgery.* St. Louis: Mosby; 1995:617.)

The goal of therapy in anovulatory women is to produce one mature follicle, sometimes two. In women with low estrogen status, cycle fecundability approaches the ideal (~20%/cycle) if there are no other infertility factors. It is a little lower, however, in women who are CC failures or have PCOS (Lunenfeld, 1995) (Fig. 40.15). The risk of hyperstimulation is greatest in these patients, and great care has to be used when monitoring them (discussed later).

By injecting gonadotropins, the physiology behind this approach is to increase the serum FSH level to more than a critical threshold level, which is an unknown at the outset. The window for this therapeutic threshold is fairly wide in normal and hypoestrogenic women, but it is extremely narrow in PCOS, increasing the risk of hyperstimulation. A starting dose of 150 IU with FSH is used (as a recombinant preparation of pure FSH or a combination of LH and FSH in a urinary preparation). The $E_2$ level is determined and ultrasound is performed after approximately 5 days and then approximately every other day until a follicle

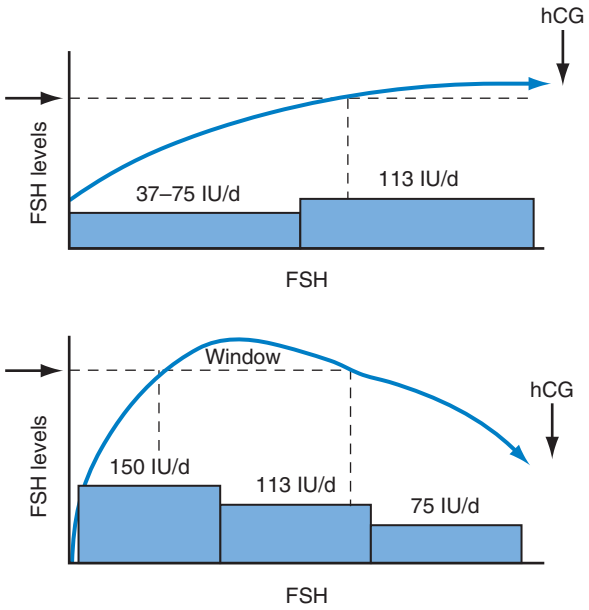



**Fig. 40.16** Schematic representation of serum follicle-stimulating hormone (FSH) levels and daily dose of exogenous FSH during low-dose step-up or step-down regimens for ovulation induction. *hCG,* Human chorionic gonadotropin. (From Macklon NS, Bart CJ. Medical approaches to ovarian stimulation for infertility. In: Strauss JF, Barbieri RL, eds. *Yen and Jaffe's Reproductive Endocrinology.* 6th ed. Philadelphia: WB Saunders; 2009:701.)

reaches a diameter of at least 18 mm. The **serum $E_2$ level should be at least in the range of 200 pg/mL for a mature follicle.** At this point, 5000 to 10,000 IU of HCG is administered IM (or pure recombinant HCG, Ovidrel, 250 μg SC) to trigger ovulation. Timed intercourse is usually advised if there is a normal semen analysis and good cervical mucus. **Ovulation should occur between 36 and 48 hours after the trigger of HCG.** Particularly in women with hypothalamic amenorrhea and low estrogen status, **vaginal progesterone supplementation (100 to 200 mg/day**) is usually prescribed, although this addition is not completely evidence-based.

In women with PCOS in whom the ovary is extremely sensitive to gonadotropin, a starting dose of only 50 to 75 IU is used. A slow step-up regimen is usually preferred, increasing the dose slowly only after 7 days (Macklon, 2009) (Fig. 40.16). Although there have been advocates for the use of a step-down approach (higher initial dose and then a rapid decrease), randomized trials in PCOS have suggested the preference for using the traditional step-up approach, which has better outcomes.

The pregnancy rate per cycle should be similar to that after CC therapy (~20%). With sufficient duration of treatment and no other infertility factors, cumulative pregnancy rates are excellent. It has been reported that the cumulative pregnancy rate after nine cycles of gonadotropin therapy is approximately 77%. These effects are influenced by age and type of anovulation as noted previously (see Fig. 40.15). The incidence of spontaneous abortion after gonadotropin therapy is higher than the normal rate (25% to 35%), and the overall multiple pregnancy rate (usually twins) is in the range of 15%, but there is a risk of this being much higher, particularly with inadequate monitoring.

### Ovarian Hyperstimulation Syndrome

Although enlarged ovaries are often encountered after gonadotropin administration, significant ovarian hyperstimulation syndrome (OHSS) occurs in **approximately 0.5% of women receiving gonadotropins; and can be as high as 10% in women with PCOS**. OHSS can be life threatening, causing massive fluid shifts, ascites, pleural effusion, electrolyte disturbances, and thromboembolism (Tan, 2013). The cause has not been completely elucidated but is related to the large cystic ovaries, high $E_2$ levels, and the ovarian elaboration of substances such as vascular endothelial growth factor (VEGF), which increases vascularity and vascular permeability. Several investigators have classified OHSS into mild, moderate, and severe forms. A representative categorization may be found in Box 40.1 (Navot, 1992). HCG triggers the syndrome, and blood levels of HCG continue to stimulate the ovaries in OHSS. Therefore the syndrome is worse if pregnancy occurs and abates within 1 week in the absence of pregnancy. For this reason, if severe OHSS is anticipated, HCG injection should be withheld. In IVF cycles, the embryos may be frozen rather than replaced to avoid pregnancy.

Treatment of OHSS is largely supportive, with judicious use of fluids (normal saline) and prevention of thrombosis. Correction of electrolyte disturbances and maintenance of urine output are of greatest importance. Occasionally, admission for intensive care unit (ICU) monitoring is necessary.

Avoidance of excessive stimulation is the primary approach for preventing OHSS. Lowering or withholding the dose of HCG is also advisable. An alternative approach is to use a GnRH agonist instead of HCG to trigger ovulation (as long as there is a normal pituitary able to release LH) because LH is much shorter acting

**BOX 40.1** Classification of Ovarian Hyperstimulation Syndrome

**MILD**

Ovarian enlargement (≤5 cm)
Abdominal discomfort

**MODERATE**

Ovarian enlargement (6-10 cm)
Nausea or gastrointestinal symptoms
Abdominal discomfort
Normal laboratory evaluation
Mild ascites, not clinically evident

**SEVERE**

Symptoms as above and other symptoms, such as respiratory distress
Ovarian enlargement
Severe ascites (clinically evident)
Hydrothorax
Elevated hematocrit (>45%)
Elevated WBC count (>15,000/μL)
Elevated creatinine
Electrolyte abnormalities (hyponatremia, hyperkalemia)
Elevated liver function tests

**Critical (as a subcategory of severe)**

Severe end organ dysfunction
  Oliguria, creatinine >1.6 mg/dL
  Severe respiratory distress
Thrombotic complications
Infection
Severe hemoconcentration
  Hematocrit >55%
  WBC count >25,000/μL

Modified from Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil Steril.* 1992;58(2):249-261.
*WBC,* White blood cell.

and will clear from the circulation soon after ovulation. An approach to treat OHSS is the use of a dopamine agonist such as cabergoline, which interferes with the action of VEGF. Meta-analysis has shown this to be beneficial (Tang, 2012). Metformin use in women with PCOS, in the setting of IVF, has also been shown to decrease the risk of OHSS.

The majority of studies and meta-analyses have not shown a statistically significant increased risk of ovarian or breast cancer in women receiving gonadotropin therapy (Diergaarde, 2014).

### Gonadotropin-Releasing Hormone

An alternative to the administration of gonadotropins is GnRH treatment, particularly in estrogen-deficient women. Because continuous administration of GnRH will saturate the receptors and thus inhibit gonadotropin release to induce ovulation, GnRH must be administered in a pulsatile manner, as occurs normally, at intervals of 60 to 90 minutes. GnRH is a peptide, so it cannot be administered orally; the two methods of administration in current use are the intravenous (IV) and subcutaneous routes. More drug must be administered by the subcutaneous route than by the IV route; however, the subcutaneous route avoids use of an indwelling IV catheter, with its accompanying problems. The success rates, however, are better with IV delivery. The medication is given by means of a small portable pump, which is usually worn attached to an article of clothing. Ovulation rates of approximately 75% to 85% per treatment cycle have been reported; however, this approach is cumbersome, requiring a continuous line and a portable pump 24 hours a day. It is not often used.

## Other Therapeutic Modalities

### Weight and Lifestyle Management

Particularly in women who are clomiphene resistant, weight loss will often ameliorate the situation. In overweight women it is important to ensure that abnormalities in glucose and lipid metabolism are normalized as much as possible before induction of ovulation. There is evidence that lifestyle changes in diet and exercise may improve overall fitness and metabolic parameters, as well as ovulatory responses, even in the absence of true weight loss, although there could be a redistribution of body fat with lifestyle changes.

### Ovarian Electrocauterization

At a European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus meeting in Thessaloniki, Greece for the treatment of infertility in PCOS, it was concluded that a possible alternative to gonadotropin therapy in clomiphene-resistant women with PCOS is the use of ovarian electrocautery, which has similar efficacy (Thessaloniki ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2008).

Laparoscopic electrical or laser-generated burn holes through the ovarian cortex have been associated with improving ovulation rates, as was described many years ago with ovarian wedge resection, which is no longer performed. The major advantage of this more invasive method of ovarian electrocauterization is that it decreases the risk of hyperstimulation and multiple pregnancies. In addition to a concern of surgical complications, excessive destruction of the ovarian cortex can lead to premature ovarian failure. Only a limited number of burn holes (~10) should be made.

It has been reported that the endocrine changes may persist for at least 10 years (Gjonnaess, 1998). A Cochrane review has also reported an overall term pregnancy rate of 50% after surgery and a low multiple pregnancy rate (Farquhar, 2005).

Nevertheless, ovulation induction in women with PCOS should still be a medical treatment, particularly with the use of adjuncts if necessary. In our view, ovarian electrocauterization should be reserved for patients who have difficulties with gonadotropin stimulation (failure of dominant follicle selection or hyperstimulation risk) even in the setting of IVF, which is usually the next step in women who tend to have hyperstimulation with gonadotropin induction of ovulation.

## Male Factor Infertility

### The Male Evaluation

If the semen analysis is abnormal and has been repeated, it is important that the man be evaluated by an andrologist, usually a urologist. Important medical conditions must be ruled out, and occasionally an abnormality is found that can be treated. Blood should be obtained for hormone and other testing, as needed, and a careful urologic examination can diagnose problems such as testicular abnormalities and infection (Fig. 40.17). The more treatable conditions are hormonal abnormalities (apart from an elevated FSH level, signifying end organ seminiferous failure) and infection. **Varicocele** repair remains somewhat controversial, and the decision must be individualized based on the ages of the couple, other factors that may be involved, and whether the *varicocele is symptomatic, or at least clinically detected (palpable)*. Although a varicocele has been **shown to correlate with poor sperm characteristics, there is often a variable response to surgery**. It is important to note that improvement may not be evident for 6 months, given that the cycle of spermatogenesis is approximately 3 months in length (Practice Committee ASRM, 2014).

In the most common findings of oligo-, astheno-, or teratospermia, it is important to know how the man should be evaluated. Fig. 40.18 provides a suggested algorithm (Bach, 2019).

If the evaluation is nondiagnostic or if no treatment is possible or indicated, the best therapy should be directed at improving the

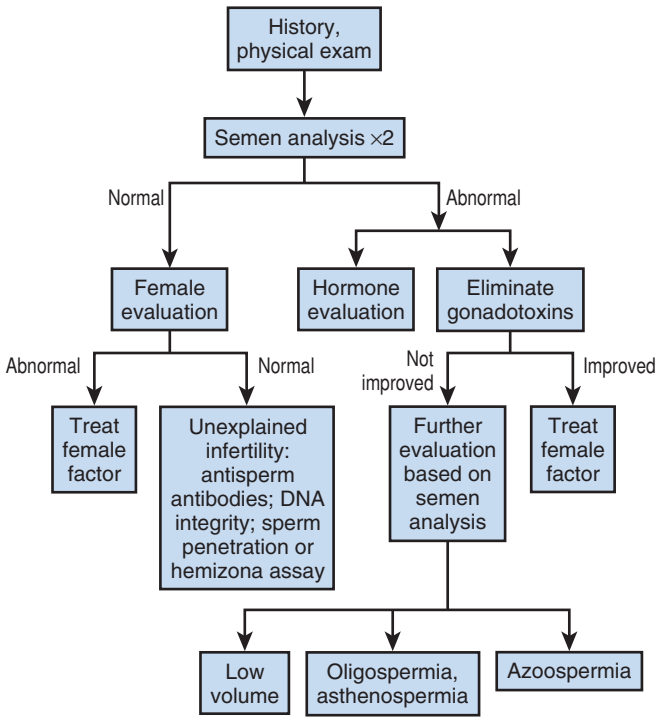



**Fig. 40.17** General algorithm for the diagnostic evaluation of male infertility. (From Turek PJ. Practical approaches to the diagnosis and management of male infertility. *Nat Clin Pract Urol.* 2005;2:226-238.)

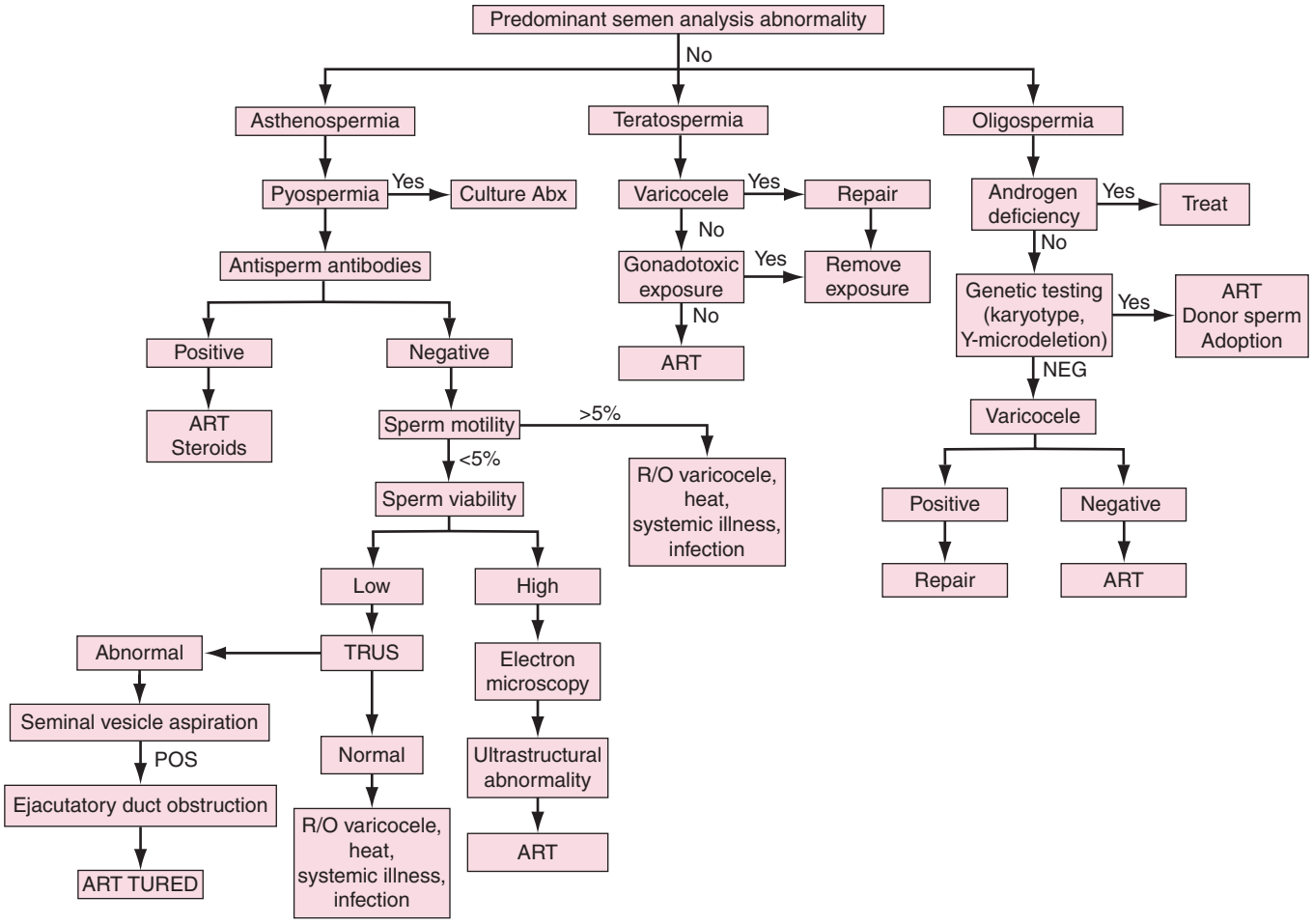



**Fig. 40.18** Algorithm for the evaluation and management of men with oligoasthenoteratospermia. *Abx,* Antibiotics; *ART,* assisted reproductive technology; *NEG,* negative; *POS,* positive; *R/O,* rule out; *TRUS,* transrectal ultrasound; *TURED,* transurethral resection of the ejaculatory ducts. (From Bach PV, Schlegel PN. Male infertility. In: *Yen and Jaffe's Reproductive Endocrinology.* 8th ed. Philadelphia: Elsevier; 2019:586.)

ejaculate for IUI or to carry out IVF with ICSI. IUI has been used to treat oligospermia and abnormalities of semen volume or viscosity to enhance fecundability. The limitation of successful IUI is when there is significant oligospermia or motility problems (less than 5 million motile sperm available) or with very poor morphology. Data, however, have suggested that abnormal morphology alone may not affect the success of IUI treatment (Deveneau, 2014), and abnormal morphology has been found often in previously fertile men.

The procedure of IUI (after washing and centrifugation of the ejaculate) is associated with higher pregnancy rates if combined with COS than when used in natural ovulatory cycles. IUI is also of benefit to women with variable degrees of cervical stenosis. Ideally insemination should take place on the day of or just before ovulation. It is advisable to use a urinary LH kit to determine the optimal date to perform insemination because the urinary LH peak occurs on the day before ovulation. Insemination should be scheduled for the morning after LH is initially detected in an afternoon urine specimen. In women who have difficulty with LH kits, or empirically, ovulation may be "triggered" with HCG injection (typically 250 μg of recombinant HCG Ovidrel SC), as long as follicular development is adequate (typically at least a 20-mm follicle on ultrasound).

Separation of sperm from the seminal fluid by double centrifugation, the swim-up technique, or use of a density gradient should be performed before IUI. This enhances sperm motility and is thought to increase capacitation (membrane changes in sperm that facilitate fertilization). IUI of unwashed seminal fluid should not be used because it may cause infection and can produce severe uterine cramps as a result of prostaglandin content in seminal fluid.

Until rather recently, if there were severe abnormalities in the semen analysis, the prognosis for fertility was less than that for any other cause of infertility (see Fig. 40.8), even with the use of IVF techniques. Attempts to enhance fertilization rates of aspirated oocytes with the technique of subzonal insemination of sperm were unsuccessful because fertilization rates remained low, approximately 15%. After Van Steirteghem and associates developed the technique of **ICSI**, fertilization rates of oocytes injected with a single normal sperm obtained from men with severe abnormalities in their semen analysis increased to more than 50% (Van Steirteghem, 1993). **Pregnancy rates per ET are now similar after ICSI compared with other indications for IVF.** When there is very low or no sperm in the ejaculate, IVF/ICSI can be carried out using testicular sperm (see Chapter 41).

Some couples, particularly those whose male partner has azoospermia, may choose to use donor sperm insemination. If they choose this option, the attitudes of both partners regarding the use of donor semen and the stability of the marriage must be thoroughly discussed before the procedure is performed. Donors from sperm banks are carefully screened for infectious diseases, and all semen samples are quarantined for at least 6 months

because of the long time it takes for positive antibodies to HIV to appear after infection. ASRM has published a set of guidelines for semen donor insemination. These guidelines provide information regarding indications for donor insemination and suggested procedures for selection and screening of possible semen donors.

Freezing of sperm is the only way that donor insemination should be done because of the time necessary to quarantine samples to rule out infectious diseases, but freezing sperm affects fecundability. A cumulative pregnancy rate after insemination of approximately 50%, and a monthly fecundity rate of only 9% has been reported after 6 months of treatment; however, the range is variable and may be as high as a fecundity rate of 18%, with a 45% cumulative pregnancy rate at 3 months. There is a known variability of semen quality after thawing, even in normal fertile sperm donors.

## Uterine Causes of Infertility

In the evaluation of the uterus by HSG, a number of **filling defects** may be appreciated. These are usually polyps, submucous fibroids, or intrauterine adhesions. This imaging can also be assessed by saline sonography (SIS) and ultimately with hysteroscopy where findings can be treated.

### Intrauterine Adhesions/Synechiae

In addition to menstrual abnormalities and recurrent abortion, some women may not be able to conceive because of the presence of intrauterine adhesions (IUAs). Most women with IUAs have had a previous event affecting the uterus, typically a previous curettage of the uterine cavity, often during or shortly after a pregnancy. If the only abnormal finding in the infertility investigation is the presence of IUAs, the prognosis for conception after hysteroscopic lysis of the adhesions is good. March and Israel reported that of 69 infertile women with IUAs and no other infertility factors, 52 (75%) conceived after hysteroscopic treatment (March, 1981).

### Leiomyoma

Congenital uterine defects rarely cause infertility, and the uterine anomalies associated with maternal ingestion of diethylstilbestrol (DES) have not been shown in randomized studies to be a cause of infertility. It is also difficult to assess the effect of leiomyomas on conception because many women with leiomyomas have no difficulty conceiving; however, depending on their location, fibroids may decrease the chance of conception or increase the miscarriage rate**. Data indicate a global change in endometrial receptivity, even with intramural fibroids** (Rackow, 2010). If no other cause of infertility is found and myomas of moderate size and position are present, a myomectomy is justified. More recent data from the IVF literature point to a **decreased pregnancy rate with submucous fibroids, and larger intramural fibroids (>4 cm)**, but in those (intramural and subserosal fibroids) that do not distort the cavity, the pregnancy rate is not affected (Sunkara, 2010). *The overall pregnancy rate after myomectomy in women with no other causes of infertility has been found to be significantly improved in retrospective studies; surprisingly there are no prospective studies showing a benefit of myomectomy.*

### Tuberculosis

Although rare in the United States, genital tuberculosis should be kept in mind. If HSG reveals findings consistent with pelvic tuberculosis, endometrial biopsy and culture should be performed to confirm the diagnosis. The radiographic features of pelvic tuberculosis that are almost diagnostic include the following: (1) calcified lymph nodes or granulomas in the pelvis; (2) tubal obstruction in the distal isthmus or proximal ampulla, sometimes resulting in a pipe stem configuration of the tube proximal to the obstruction; (3) multiple strictures along the course of the tube; (4) irregularity to the contour of the ampulla; and (5) deformity or obliteration of the endometrial cavity without a previous curettage (Fig. 40.19). Appropriate antituberculosis medication should be initiated, but women with pelvic tuberculosis should be considered sterile because pregnancies after therapy are rare. Tubal reconstructive surgical procedures are therefore not indicated. If tuberculosis is present in the tube but not in the uterus, pregnancies have been reported after IVF.

### Tubal Causes of Infertility

Since the 1980s, the incidence of infertility caused by damage to the fallopian tube has increased because of an increased incidence of salpingitis. Obstructions occur at the distal or proximal portion of the tube and sometimes in both regions. Distal obstruction leading to a hydrosalpinx (Fig. 40.20) is much more common than proximal obstruction. The prognosis for fertility after surgical tubal reconstruction depends on the amount of damage to the tube and the location of the obstruction. If there

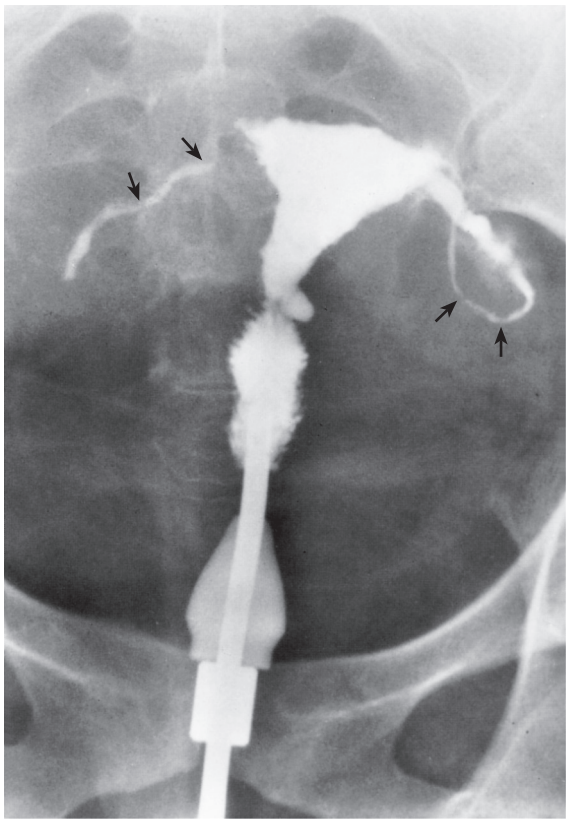


**Fig. 40.19** Tuberculous salpingitis in 37-year-old nulligravida with primary infertility for 15 years. Right tube is obstructed in the zone of transition between the isthmus and the ampulla. *Arrows* indicate multiple strictures in both tubes. Nodular contour of endometrial cavity may also be related to tuberculosis and is analogous to the pattern found in the ampulla in other cases. Small diverticulum near internal os probably represents adenomyosis. Diagnosis of tuberculosis was confirmed by endometrial culture. (From Richmond JA. Hysterosalpingography. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology.* 3rd ed. Cambridge, MA: Blackwell Scientific; 1991.)

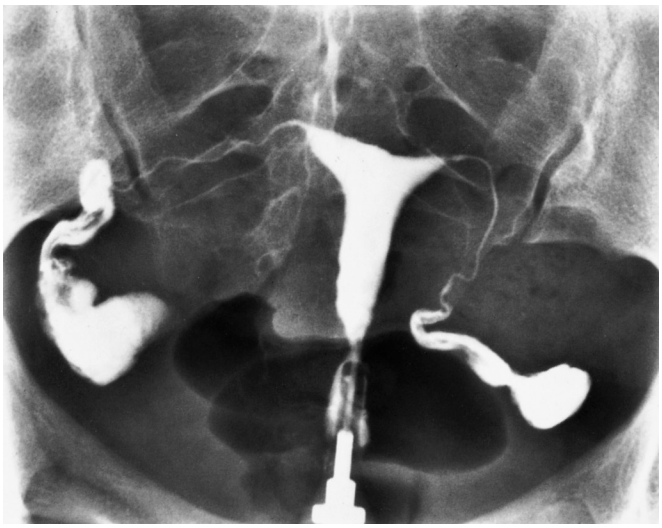


**Fig. 40.20** Hysterosalpingography showing bilateral hydrosalpinges with dilation, clubbing, and obstruction at fimbriated ends. Patient was 32-year-old woman with 10-year history of primary infertility. (From Richmond JA. Hysterosalpingography. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology.* 3rd ed. Cambridge, MA: Blackwell Scientific; 1991.)

is extensive damage, conception after tubal reconstruction is unlikely. Women with extensive tubal disease have a greater chance of conceiving with an IVF procedure, so the extent and location of the intrinsic and extrinsic tubal disease should be ascertained by HSG and possibly laparoscopy in an effort to determine whether tubal reconstruction or IVF offers the better prognosis (Practice Committee ASRM, 2012b). As noted, **if a large hydrosalpinx is seen at the time of HSG, it is best to suggest that the woman have IVF rather than undergo tubal reconstructive surgery. It is recommended that the hydrosalpinx be excised before IVF if it is large and visible by ultrasound**. If proximal and distal obstructions of the tube exist, the damage to the tube is usually so extensive that the tube cannot function normally. Therefore although it is possible to achieve tubal patency after surgical repair with proximal and distal blockage, subsequent intrauterine pregnancy is uncommon and surgical reconstruction should not be performed in such cases. In general, infertility surgery for tubal disease is a dying art—the pregnancy rates with IVF are far superior, and most women would prefer to avoid surgery as long as they have insurance coverage for IVF.

## Distal Tubal Disease

HSG can help determine whether the tubal obstruction is complete or partial, the size of the distal sacculation, and the appearance of the mucosal folds and rugal pattern of the endosalpinx (see Fig. 40.20). Laparoscopy will assist in determining the size of the hydrosalpinx, amount of muscularis, and thickness of the wall of the tube after distention with dye. Laparoscopic examination will determine whether pelvic adhesions are present and the extent of these adhesions. Women with fimbrial obstruction are not a homogeneous group, and the prognosis for intrauterine pregnancy after distal tubal reconstruction is related to the extent of the disease process. Therefore it is important to perform HSG and laparoscopy before surgical reconstruction to provide an individualized prognosis.

If the fimbriae of the distal end of the tube are relatively normal, with only partial occlusion by adhesions or fimbrial bridges, removal of these adhesions by means of a fimbrioplasty procedure will result in higher conception rates (~60%) than if the distal end is completely occluded and a cuff salpingostomy procedure is required. Overall conception rates after salpingostomy are in the 30% range, with a high percentage (~25%) being tubal pregnancies. Although microsurgical techniques had been used for all tubal infertility surgery, all procedures are carried out via laparoscopy. **The incidence of ectopic pregnancy after surgical reconstruction for distal tubal disease is directly related to the amount of tubal damage** existing before the operative procedure; however, **today less and less primary tubal reconstructive surgery is being done.**

The results of tubal reconstruction correlate with the degree of tubal damage according to the severity of five factors: (1) extent of adhesions, (2) nature of adhesions, (3) diameter of the hydrosalpinx, (4) appearance of the endosalpinx, and (5) thickness of the tubal wall, with the latter being the best correlated. Using these criteria, prognostic categories have been identified: good, with a cumulative pregnancy rate of approximately 75%; intermediate, approximately 20%; and poor, less than 5%. In the good category, only 1 of 22 pregnancies may be ectopic, but in the intermediate group, 50% of the pregnancies may be expected to be tubal. **In the poor prognostic group, most of the pregnancies will be ectopic**. Accordingly, in women with fixed adhesions, with absent rugal folds and a thick, fixed tubal wall, distal tubal reconstructive surgery probably should not be performed.

## Proximal Tubal Blockage

If no dye enters the tube during HSG, the diagnosis of proximal tubal blockage is likely; however, because spasm of the uterus during the procedure may occlude the intrauterine portion of the tube, the diagnosis cannot be confirmed. Here, at least half of the time, the tube will be found to be patent on subsequent testing or at laparoscopy. Laparoscopy also allows examination of the distal portion of the tube, which cannot be visualized radiographically if there is proximal blockage.

It is preferred to attempt selective catheterization of the proximal portion of a tube at HSG under fluoroscopy if it does not fill with dye (Thurmond, 2008) (see Fig. 42.7). Cannulation of the proximal portion is also possible under direct guidance at hysteroscopy. Cannulation to open the putative obstruction is possible as long as there is no gross disease visible, such as salpingitis isthmica nodosa (SIN). Proximal tubal blockage may be caused by debris or endometriosis, but a significant occlusion is usually explained by prior infection or SIN.

In the past, proximal obstructions were best handled by microsurgical cornual tubal reanastomosis, with pregnancy rates in the range of 50% and ectopic rates of only 10%. Although this approach may still be considered on a selective basis, ***most cases of obstruction not relieved by fluoroscopic or hysteroscopic selective cannulation are now treated by IVF.***

## Adjunctive Therapy After Tubal Surgery

Adjunctive procedures for surgical tubal reconstruction previously included prophylactic antibiotics, intraperitoneal corticosteroids, postoperative hydrotubation, and placement of tubal stents. Prospective studies have not demonstrated postoperative hydrotubation to have any benefit, and tubal stents should not be used because they may cause mucosal damage. Data from several studies have shown that **intraperitoneal adjuncts are not effective.**

The only barriers currently used with some efficacy are an absorbable adhesion barrier (Gynecare Interceed, Ethicon), to be used only in areas that are dry and not bleeding, and barriers impregnated with hyaluronic acid (Seprafilm, Genzyme). The latter can be used as a slurry at the end of laparoscopy. Gore-Tex requires suturing and removal; therefore it is rarely used and is not applicable for tubal disease.

If pregnancy does not occur within 6 to 12 months after tubal reconstruction, HSG should be performed. **If tubal obstruction has recurred, a repeat surgical procedure is not advised**. In this setting, the pregnancy rates are less than 10%.

## Endometriosis

Some investigators have estimated that as many as **40% of infertile women have endometriosis**. If endometriosis is found at the time of laparoscopy, the extent of the disease should be documented. The causes, diagnosis, and treatment of endometriosis are presented in detail in Chapter 19.

Although endometriosis is often encountered in an infertility population (20% to 40%), the diagnosis may be subtle and may only be realized if a laparoscopy is carried out. As noted, laparoscopy is often currently bypassed in the investigative workup. Thus unless there is a strong component of pain as a presenting complaint, or a large endometrioma is seen on ultrasound, the diagnosis may not be appreciated. The treatment for pain is somewhat different and is reviewed in Chapter 19.

If laparoscopy is carried out and mild lesions are seen, it makes sense to ablate them surgically by electrocauterization or laser. Although this may not have a major therapeutic value, the current thinking is that peritoneal endometriosis may release substances that could impair fertilization at various levels.

With endometriosis various structural factors, particularly adhesions, contribute to the infertility of endometriosis, and classification schemes have been used to take this into account, but classifications are not often used in a prospective manner. In general, **women with endometriosis have a reduced fecundability**. This **relates to inflammatory factors, reduction in ovarian reserve (lower AMH levels are common) and extensiveness of the disease, which relates to mechanical (obstructive) factors.**

Surgery in the setting of infertility is reserved for those patients with pain and if large endometriomas are present. Smaller, 2- to 4-cm endometriomas may be observed, particularly in older women, because of the concern of compromising ovarian reserve by ovarian cystectomy. Otherwise, women should be treated as if they have unexplained infertility (discussed later). Many women with unexplained infertility may have endometriosis that has not been diagnosed because laparoscopy was not performed. **The lowered cycle of fecundity in endometriosis is similar to that of women with unexplained infertility (~4%).** COS, generally with IUI, is the usual initial treatment. If pregnancy does not occur in three to six cycles, IVF is offered as the next step. When surgery has been offered as the primary treatment for moderate to severe disease, which is easily diagnosed, pregnancy rates of approximately 50% have been recorded with operative laparoscopy. This rate is similar to the rate after laparotomy (see Chapter 19).

IVF pregnancy rates have been suggested to be reduced, but this mainly occurs with severe disease. In select cases, prior suppression of known causes of endometriosis (e.g., using an oral contraceptive continuously or a GnRH agonist for 2 to 3 months) has been shown to improve IVF pregnancy rates. For COS, there also has been a preference for using letrozole (aromatase inhibitor), rather than CC, which results in lower estrogen levels during the cycle and may also be helpful as endometriosis lesions express aromatase.

## Unexplained Infertility

This diagnostic category is relatively arbitrary and is probably never truly unexplained. Nevertheless, it represents a large number of patients who are evaluated for infertility. Some patients **merely have reduced fecundability based on chronologic or biologic reproductive age**. Unexplained infertility is defined as couples with normal ovulation and pelvic evaluation with a normal uterus and patent tubes on hysterosalpingogram, as well as a normal semen analysis. In the past the diagnosis also required a normal PCT and a laparoscopy. Laparoscopy is no longer carried out routinely unless there are clues to significant pelvic abnormalities. The rationale for omitting laparoscopy in the required diagnostic workup is that it is invasive and costly, and it is unlikely that the subtle abnormalities will change the outcome of treatment. Some studies have included couples into the category of unexplained infertility with mild abnormalities in the semen analysis and the suggestion of mild endometriosis.

Using the broad definition of unexplained infertility, **approximately 20% of all couples will fall into this category**. If exhaustive meticulous testing is carried out, including laparoscopy, this figure has been reported to be less than 5%. Additional testing for defects in sperm function and for endometrial histologic and biochemical variables has not been validated for routine use in making the diagnosis. Subtle defects may be overcome by standard empirical treatment for unexplained infertility. **At the same time, it is likely that on more rare occasions that there are true defects at the level of sperm or oocyte**. Occult defects in sperm may only be known in the setting of IVF (Bungum, 2004), and the absence of sperm RNA elements has also been documented in normal-appearing sperm (Jodar, 2015). The finding of "defective" oocytes has also been documented (Ezra, 1992).

The routine empirical treatment of unexplained infertility is ovarian stimulation with CC or gonadotropins, coupled with IUI. Prospective studies have shown that CC alone or IUI alone is not efficacious (Bhattacharya, 2008). Several European studies have also suggested that patients with a good prognosis, based on age and shorter duration of infertility, should undergo "expectant management," meaning continued timed intercourse for another 6 months before proceeding to treatment. A prediction model for natural conception was constructed by Hunault in the Netherlands, which was based on data from three cohorts of women with subfertility. In women younger than 38 years, the prognosis was calculated based on PCT, age, duration of infertility, prior pregnancy, percentage of motile sperm, and the referral pattern. A score of 60% or more was considered to be "good" and one of 30% or lower was "poor." Patients with a good prognosis in the Netherlands have usually been assigned expectant management for 6 months. The criteria for the Humault model have been refined for greater precision and include more data, such as body mass index, FSH levels, and semen volume and morphology (Bensdor p, 2017).

This scenario is usually unacceptable for the U.S. population for social and economic reasons. Also, in Europe the standard management of unexplained infertility with CC/IUI results in a lower pregnancy rate per cycle (closer to an expectant group) because of a more conservative approach to ovarian stimulation (Custers, 2012). The efficiency of COS/IUI is highly age dependent. In women in their 30s, the expected fecundity rate is 8% to 9% and is not much different with the use of CC or gonadotropins, a conclusion that has been based on prospective data (Reindollar, 2010) (Table 40.6).

In 1998 Guzick and associates published a review of data from 45 published studies of various therapies of unexplained infertility,

**TABLE 40.6** Randomized Trial of Treatments for Unexplained Infertility

| Number of Initiated Cycles | CC/IUI | FSH/IUI | IVF |
|---|---|---|---|
| All subjects | 1294 | 700 | 622 |
| Live births per initiated cycle | 7.6% (6.2-9.2) | 9.8% (6.8-14) | 30.7% (27.1-34.5) |

Data from Reindollar RH, Regan MM, Neumann PJ, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril.* 2010;94(3):888-899.

*CC,* Clomiphene citrate; *IUI,* intrauterine insemination; *FSH,* follicle-stimulating hormone; *IVF,* in vitro fertilization.

including mild endometriosis. After adjustment for study quality, pregnancy rates per initiated treatment cycle were 1.3% to 4.1% for no treatment, 8.3% for CC plus IUI, 17.1% for gonadotropins plus IUI, and 20.7% for IVF. Although the pregnancy rate in this analysis of nonrandomized studies was higher with gonadotropins/IUI than with CC/IUI, prospective data have shown that the rates are similar as noted previously (Reindollar, 2010). IVF pregnancy rates are also higher now than they were in 1998. Although **the rate of approximately 9% per cycle may seem low, the background rate for unexplained infertility is no more than 4%; thus the fecundity is more than doubled.** In terms of the choice of CC/IUI, whereas in a patient without PCOS and with unexplained infertility, letrozole/IUI may also be used, **it appears that CC/IUI may be more effective** (Fig. 40.21). In this National Institutes of Health (NIH)–sponsored trial coined **AMIGOS**, although gonadotropins resulted in a higher pregnancy and live birth rate, there was a **high multiple pregnancy rate of 32% compared with CC** and **letrozole**, which had similar rates

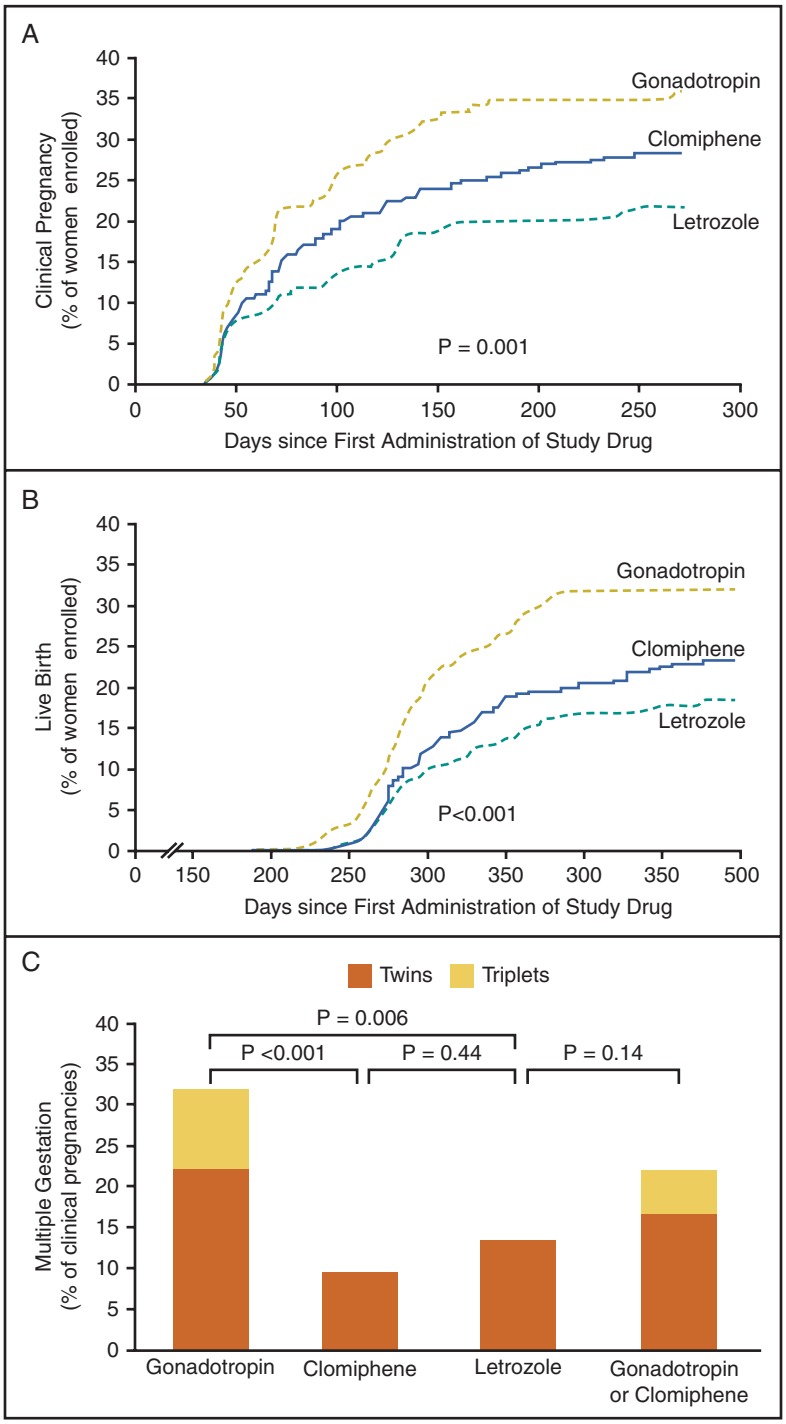
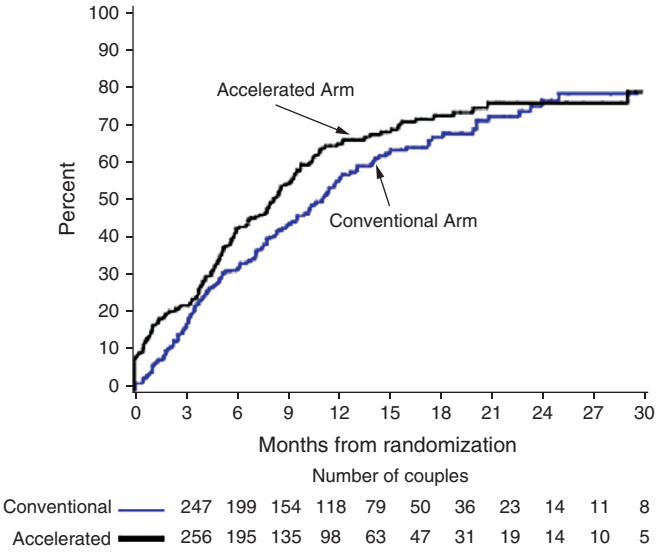



**Fig. 40.21** Pregnancy rates in the gonadotropin, clomiphene, and letrozole groups. **A,** Clinical pregnancy rates in the three groups, **B,** Live birth rates. **C,** Rates of multiple gestation. *P* values depict comparisons among the various groups. (From Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin or clomiphene for unexplained infertility. *N Eng J Med.* 2015;373(13): 1230-1240.




| Time Period (m) | Hazard Ratio | 95% CI | | P-value |
|---|---|---|---|---|
| ≤ 3 | 1.52 | 1.02 | 2.28 | 0.04 |
| > 3 to 11 | 1.40 | 1.03 | 1.90 | 0.03 |
| > 11 | 0.60 | 0.34 | 1.06 | 0.08 |

**Fig. 40.22** Randomized clinical trial to evaluate optimal treatment for unexplained infertility: The Fast Track and Standard Treatment (FASTT) trial. *CI,* Confidence interval. (From Reindollar RH, Regan MM, Neumann PJ, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: The Fast Track and Standard Treatment [FASTT] trial. *Fertil Steril.* 2010;94(3):888-899.)

(9% and 13%); letrozole did not result in a lower multiple pregnancy rate as had been hypothesized (Diamond, 2015). For this reason, gonadotropin/IUI is less commonly used in couples with unexplained infertility.

A large prospective trial was carried out by Reindollar and colleagues to assess whether it was reasonable to skip gonadotropin/IUI therapy and proceed to IVF after three cycles of CC/IUI (called *fast track*). The logical next step after CC or gonadotropin/IUI therapy is still proceeding to IVF. One of the concerns with unexplained infertility is that there may be failure to fertilize, even if there are normal ovulation and semen characteristics. IVF also has a higher cycle fecundity rate (discussed later). In the prospective trial, as shown in Fig. 40.22, there was an increased pregnancy rate in the accelerated arm (100% to 156%; hazard ratio, 1.25). The median time to pregnancy was also shorter, 8 versus 11 months, and average charges per delivery were $9800 lower. Individual per cycle pregnancy rates for CC/IUI, gonadotropin/IUI, and IVF were 7.6%, 9.8%, and 30%, respectively (Reindollar, 2010). **The conclusion of these authors was that the gonadotropin/IUI step in the usual algorithm for unexplained infertility may be omitted**. Age is a significant factor in terms of efficacy of treatment. Table 40.7 shows the results of a large retrospective study of the success of CC/IUI according to age (Dovey, 2008). It is clear that in older women, because of reduced efficacy (**after age 42, cumulative pregnancy rates over 3 to 9 months are approximately 1.8%), couples should consider going directly to IVF.** In a follow-up study by Reindollar in a slightly older population (38 to 42 years), it was concluded that in this group, going directly to IVF is probably a better option (Goldman, 2014).

**TABLE 40.7** Realistic Chances of Pregnancy With Intrauterine Insemination: Age Dependency*

| Age of Woman (yr) | Pregnancy Rate per Cycle (%) |
|---|---|
| <35 | ≈10-11.5 |
| 35-37 | ≈8.2-9.2 |
| 38-40 | ≈6.5-7.3 |
| 40-41 | ≈3.6-4.3 |
| >42† | ≈0.8-1.0 |

From Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles. *Fertil Steril.* 2008;90(6):2281-2286.
*Large cohort of 4100 cycles of CC IUI.
†In women older than 42 years, cumulative pregnancy rates = 1.8% (1 in 55).
*CC,* Clomiphene citrate; *IUI,* intrauterine insemination.

Cycle fecundity may be reduced substantially, even in women younger than 40 years who have a low ovarian reserve. Accordingly, it is important to measure day 2 to 3 FSH levels as well as AMH and an AFC. Low parameters will help dictate how aggressive treatment should be, with many couples being directed toward IVF as a primary treatment. Because of the importance of IVF as a treatment option in current infertility management, a separate chapter is devoted to IVF and newer therapies (see Chapter 41).

## PREGNANCY OUTCOMES IN WOMEN TREATED FOR INFERTILITY

**Ovulation-inducing drugs and reconstructive tubal surgery** have independently been shown to be associated with an ***increased incidence of ectopic pregnancy*** compared with the normal population. Use of ovulation-inducing drugs alone has been shown to increase the incidence of multiple gestations. With IVF the chances of multiple gestations is better controlled based on the decision to transfer only one embryo (see Chapter 41); however, IVF does increase the risk of ectopic pregnancies, with a higher rate based on the number of embryos transferred (Perkins, 2015). There is also an increase in the risk of heterotopic pregnancies; therefore, if conception occurs after treatment with ovulation induction or tubal reconstructive surgery, monitoring of early gestation with serial HCG levels and ultrasonography assists in determining whether the pregnancy is intrauterine and how many gestational sacs are present; however**, infertile couples who conceive do not have a higher rate of spontaneous abortion or perinatal mortality than normal couples. Compared with the noninfertile population, the fetal malformation rate is slightly increased**. In all older women, there is a higher pregnancy loss rate because of aneuploidy.

## COUNSELING AND EMOTIONAL SUPPORT

The diagnosis of infertility can be a devastating and life-altering event that affects many aspects of a woman's life. Infertility and its treatment can affect a woman and her spouse or partner medically, financially, socially, emotionally, and psychologically. Feelings of anxiety, depression, isolation, and helplessness are not uncommon in women undergoing infertility treatment. Strained and stressful relationships with spouses, partners, and other loved ones occur among patients undergoing infertility treatment as treatment gets underway and progresses.

It is important that every program address the emotional and social needs of couples undergoing treatment. Individual counseling

and support groups, as well as patient information sessions, should be part of every infertility practice. National support groups such as the National Infertility Association (RESOLVE, www.prnewswire.com) and the American Fertility Association (www.theafa.org) are also available to provide assistance and information. ASRM also has many educational resources, specifically designed for patients with a separate portal available at the society's website (www.asrm.org). Patient-oriented videos are available regarding various aspects of infertility at www.reproductivefacts.org.

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**Suggested readings for this chapter can be found on ExpertConsult.com.**

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