

mild-to-moderate endometriosis, and/or borderline semen parameters, a stepwise approach to infertility is optimal, beginning with low-risk interventions and moving to more invasive, higher risk interventions only if necessary. After determination of all infertility factors and their correction, if possible, this approach might include, in increasing order of complexity: (1) expectant management, (2) clomiphene citrate or an aromatase inhibitor (see below) with or without intrauterine insemination (IUI), (3) gonadotropins with or without IUI, and (4) in vitro fertilization (IVF). The time used for evaluation, correction of problems identified, and expectant management can be longer in women age <30 years, but this process should be advanced rapidly in women age >35 years. In some situations, expectant management will not be appropriate.

OVULATORY DYSFUNCTION

Treatment of ovulatory dysfunction should first be directed at identification of the etiology of the disorder to allow specific management when possible. Dopamine agonists, for example, may be indicated in patients with hyperprolactinemia (Chap. 403); lifestyle modification may be successful in women with obesity, low body weight, or a history of intensive exercise.

Medications used for ovulation induction include agents that increase FSH through alteration of negative feedback, gonadotropins, and pulsatile GnRH. *Clomiphene citrate* is a nonsteroidal estrogen antagonist that increases FSH and LH levels by blocking estrogen negative feedback at the hypothalamus. The efficacy of clomiphene for ovulation induction is highly dependent on patient selection. In appropriate patients, it induces ovulation in ~60% of women with PCOS and has traditionally been the initial treatment of choice. Combination with agents that modify insulin levels such as metformin does not appear to improve outcome. Clomiphene citrate is less successful in patients with hypogonadotropic hypogonadism. *Aromatase inhibitors* have also been investigated for the treatment of infertility. Studies suggest they may have advantages over clomiphene, but these medications have not been approved for this indication.

Gonadotropins are highly effective for ovulation induction in women with hypogonadotropic hypogonadism and PCOS and are used to induce the development of multiple follicles in unexplained infertility and in older reproductive-age women. Disadvantages include a significant risk of multiple gestation and the risk of ovarian hyperstimulation, particularly in women with polycystic ovaries, with or without other features of PCOS. Careful monitoring and a conservative approach to ovarian stimulation reduce these risks. Currently available gonadotropins include urinary preparations of LH and FSH, highly purified FSH, and recombinant FSH. Although FSH is the key component, LH is essential for steroidogenesis in hypogonadotropic patients, and LH or human chorionic gonadotropin (hCG) may improve results through effects on terminal differentiation of the oocyte. These methods are commonly combined with IUI.

None of these methods are effective in women with premature ovarian failure, in whom donor oocyte or adoption is the method of choice.

TUBAL DISEASE

If hysterosalpingography suggests a tubal or uterine cavity abnormality or if a patient is age ≥ 35 at the time of initial evaluation, laparoscopy with tubal lavage is recommended, often with a hysteroscopy. Although tubal reconstruction may be attempted if tubal disease is identified, it is generally being replaced by the use of IVF. These patients are at increased risk of developing an ectopic pregnancy.

ENDOMETRIOSIS

Although 60% of women with minimal or mild endometriosis may conceive within 1 year without treatment, laparoscopic resection or ablation appears to improve conception rates. Medical management of advanced stages of endometriosis is widely used for symptom control but has not been shown to enhance fertility. In moderate and severe endometriosis, conservative surgery is associated with

pregnancy rates of 50 and 39%, respectively, compared with rates of 25 and 5% with expectant management alone. In some patients, IVF may be the treatment of choice.

MALE FACTOR INFERTILITY

The treatment options for male factor infertility have expanded greatly in recent years (Chap. 411). Secondary hypogonadism is highly amenable to treatment with gonadotropins or pulsatile gonadotropin-releasing hormone (GnRH) where available. In vitro techniques have provided new opportunities for patients with primary testicular failure and disorders of sperm transport. Choice of initial treatment options depends on sperm concentration and motility. Expectant management should be attempted initially in men with mild male factor infertility (sperm count of 15 to 20×10^6 /mL and normal motility). Moderate male factor infertility (10 to 15×10^6 /mL and 20–40% motility) should begin with IUI alone or in combination with treatment of the female partner with ovulation induction, but it may require IVF with or without intracytoplasmic sperm injection (ICSI). For men with a severe defect (sperm count of $<10 \times 10^6$ /mL, 10% motility), IVF with ICSI or donor sperm should be used. If ICSI is performed because of azoospermia due to congenital bilateral absence of the vas deferens, genetic testing and counseling should be provided because of the risk of cystic fibrosis.

ASSISTED REPRODUCTIVE TECHNOLOGIES

The development of assisted reproductive technologies (ARTs) has dramatically altered the treatment of male and female infertility. IVF is indicated for patients with many causes of infertility that have not been successfully managed with more conservative approaches. IVF or ICSI is often the treatment of choice in couples with a significant male factor or tubal disease, whereas IVF using donor oocytes is used in patients with premature ovarian failure and in women of advanced reproductive age. Success rates are influenced by cause of infertility and age, varying between 15 and 40%. Success rates are highest in anovulatory women and lowest in women with decreased ovarian reserve. In the United States, success rates are higher in white than in black, Asian, or Hispanic women. Although often effective, IVF is expensive and requires careful monitoring of ovulation induction and invasive techniques, including the aspiration of multiple follicles. IVF is associated with a significant risk of multiple gestation, particularly in women age <35, in whom the rate can be as high as 30%, which has led to specific recommendations for numbers of embryos or blastocysts to transfer based on age and specific prognostic factors.

CONTRACEPTION

Although use of contraception worldwide has increased in the last two decades, as of 2010, 146 million women worldwide age 15–49 years who were married or in a union had an unmet need for family planning. The absolute number of married women who use contraception or have an unmet need for family planning is projected to grow from 900 million (876–922 million) in 2010 to 962 million (927–992 million) in 2015.

Only 15% of couples in the United States report having unprotected sexual intercourse in the past 3 months. However, despite the wide availability and widespread use of a variety of effective methods of contraception, approximately one-half of all births in the United States are the result of unintended pregnancy. Teenage pregnancies continue to represent a serious public health problem in the United States, with >1 million unintended pregnancies each year—a significantly greater incidence than in other industrialized nations.

Of the contraceptive methods available (Table 414-1), a reversible form of contraception is used by >50% of couples, whereas sterilization (male or female) has been used as a permanent form of contraception by over one-third of couples. Pregnancy termination is relatively safe when directed by health care professionals but is rarely the option of choice.