CME CREDIT

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What the internist needs to know about infertility

ABSTRACT

Primary care physicians can manage two thirds of cases of suspected infertility. Assisted reproductive technology can help in many cases of pelvic adhesive disease, although the effectiveness of these procedures declines significantly with patient age. Testing for ovarian reserve is an important first step for many patients who are considering infertility treatment. Some causes of infertility are associated with significant medical problems such as diabetes and abnormal lipids; these should be assessed and a long-term management plan implemented.

KEY POINTS

Measurements of serum levels of follicle-stimulating hormone (FSH) and estradiol on the third day of the menstrual cycle can help predict if a woman will respond to fertility treatment.

Male-factor infertility, once untreatable, can be circumvented with in vitro fertilization and intracytoplasmic sperm injection, with excellent pregnancy rates.

Anovulation is often caused by polycystic ovary syndrome (PCOS), a metabolic disorder with a primarily reproductive clinical presentation. PCOS is often associated with insulin resistance and an abnormal lipid profile.

PATIENT INFORMATION
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PRIMARY CARE PHYSICIANS can play a major role in providing infertility services. The Centers for Disease Control and Prevention reported that in 1995, 15% of women (more than 9 million) between the ages of 15 to 44 received some sort of infertility service.[1] Of these, two thirds merely required advice or testing, which a primary care physician could provide. Only one third sought treatment such as ovulation induction, surgery, or assisted reproductive technology. Furthermore, many causes of infertility are associated with significant medical problems that a primary care physician should manage.

This article reviews the common causes of infertility, discusses an approach to assessment for primary care physicians, and updates clinicians on the latest options in reproductive technology.

INFERTILITY DEFINED

Textbooks define infertility as the inability to conceive after 1 year of unprotected intercourse. In practice we are more flexible: we would treat a patient with an obvious problem of anovulation or obstructed fallopian tubes even if she has not been trying to become pregnant for a full year.

Common causes of infertility, in approximate order of prevalence, are:

- Pelvic disease (tubal disease and endometriosis)
- Semen abnormalities
- Disorders of ovulation
- Idiopathic infertility

Is infertility increasing?

Visits for infertility increased by 3% over the last decade. A possible reason is that infertili-

ty is truly increasing in prevalence as women are waiting longer to have a first child. Twenty percent of women now have their first child after age 35, and this delay is the main social cause of infertility. Another possible reason is that effective treatment is now available, which more people are seeking.

FERTILITY AND AGE

Advancing maternal age is an independent risk factor for infertility, as shown by studies in religious groups who do not use birth control and who have high birth rates.[2] After age 30, fertility declines substantially: by age 35 a woman has half the chance of becoming pregnant that she did at age 25. In addition, women of older reproductive age have a large number of unrecognized pregnancy losses.[3] In contrast, the age of the male partner does not affect the ability of the sperm to fertilize an oocyte.[4]

Reasons for the decline in fertility with age

Loss of ovarian reserve. Reproductive aging takes place mostly in the ovary. Over time, women progressively lose their graafian follicles, and by the time of menopause the germ cell pool is depleted. Hormonal therapy such as oral contraceptive use does not affect this loss, which accelerates in the last decade before menopause.[5]

Chromosomal abnormalities accumulate in the oocytes as women age, contributing to both the decline in fertility and the increase in pregnancy loss. Recipients of donated oocytes have rates of pregnancy and live births close to those of the age group of the donor.

Concomitant diseases increase in prevalence with age and may affect fertility.

HOW TO APPROACH HISTORY-TAKING FOR COMPLAINTS OF INFERTILITY

Talk to the couple both together and individually

Given the complex and highly charged social, psychological, and financial issues surrounding having a child, it is important to take a complete history of the couple before embarking on a series of tests.

In general, I recommend seeing the couple together. This will allow the clinician to explore a number of sensitive issues. For instance, if both partners are working, have they had the time and energy to regularly have intercourse during ovulation? Is the male partner having difficulty performing sexually during ovulation, because of conflicted feelings about having a child?

Although the couple should be seen together, I do try to take some time to see each partner individually. This will give them the chance to report portions of their history that they may not have disclosed to their partner, such as a history of a sexually transmitted disease or abortion, or in the case of some second marriages, an undisclosed vasectomy.

The approach should also be individualized for each patient. Before embarking on testing, I would ensure that a healthy couple in their early 20s try for a full year to become pregnant. However, for a woman in her late 30s experiencing irregular periods, I would be more aggressive in testing.

A STRATEGY FOR INVESTIGATION OF THE INFERTILE COUPLE

The investigation of the infertile couple reflects the possible causes of infertility. The basic investigation for all infertile couples includes:

- Semen analysis
- A hysterosalpingogram
- Measurment of day-3 serum FSH and estradiol levels or a clomiphene challenge test
- An assessment of ovulation by measuring the progesterone level during the luteal phase.

I recommend performing most of these tests simultaneously. It is not unusual for infertility to stem from several causes and it is a disservice to the patient to concentrate on an obvious problem, such as polycystic ovary syndrome or suspected tubal disease, only to overlook another problem with either partner.

Subsequent evaluation is based on the test results. Most abnormal results will require referral for treatment but the primary care physician can counsel patients on treatment options, which is all that most patients want.

A discussion with the couple should include environmental factors that may affect fertility. Smoking and heavy use of marijuana

decrease fertility in both men and women. Some studies have also shown that high caffeine intake is also associated with delayed conception.[6] Most lubricants sold in pharmacies are spermicidal, as is saliva.

ASSESSING OVARIAN RESERVE IN OLDER WOMEN

Many reproductive endocrinologists feel that the following groups of infertile women should undergo an assessment of ovarian reserve:

- All infertile women older than 34 years
- Younger women who have a history of ovarian surgery, a poor response to previous infertility treatment, or a family history of early menopause
- Women who have received gonadotoxic drugs
- Women with no detectable cause of infertility (idiopathic infertility)
- Patients about to begin intensive infertility treatment such as in vitro fertilization.

There are two commonly used tests of ovarian reserve: the day-3 follicle-stimulating hormone (FSH) level and the clomiphene challenge test.[7] Both rely on measuring serum levels of FSH. If the FSH level is elevated, then the probability of achieving pregnancy is reduced.

The prognostic significance of these tests depends on the assay used. Therefore it is important to make sure that the laboratory meets the published criteria for coefficient of variation of the endocrine assays.

The day-3 FSH test

The day-3 FSH test consists of measuring the serum level of FSH on the third day of the menstrual cycle. In practice, the test is equally valid if performed on days 2, 3, or 4. Numerous studies have shown that at most, only 5% of women with an elevated FSH level succeed in conceiving with in vitro fertilization.[7] Upper limits used range from 11 to 14 IU/L. The test has been validated in patients who were about to undergo superovulation for in vitro fertilization or insemination, not in a general infertile population. An abnormal test result is associated with a poor pregnancy rate irrespective of age.

On the other hand, a normal test result does not mean that a patient will achieve pregnancy with in vitro fertilization. The most recent data for in vitro fertilization success rates (from 1997) is available through the Centers for Disease Control and Prevention (www.cdc.gov/nccdphp/drh/art97/index.htm). The live birth rates per 100 cycles initiated are 31% for women under 35 years of age, 26% for women 35 to 37 years of age, 17% for women 38 to 40 years of age, and 8% for women over 40 years of age. Therefore, the test has a poor sensitivity because it does not screen for most of the patients that will not achieve a pregnancy.

The clomiphene challenge test

The clomiphene challenge test is a more sensitive test of ovarian reserve: in studies,[7,8] twice as many patients were identified as poor responders with the clomiphene challenge test than with a day-3 FSH level alone. In the clomiphene challenge test the patient has her FSH level measured on the third day of her menstrual cycle, and then takes clomiphene citrate (Clomid, Serophene; an antiestrogen) 100 mg daily on days 5 through 9 and has her FSH level measured again on day 10. Results are considered abnormal if any level is higher than 10 to 12 IU/L.[8,9]

Alternatively, the day 3 and day 10 serum FSH levels can be added together. In a series by Loumaye et al,[10] no woman became pregnant who had a summed FSH level greater than 26.

The clomiphene challenge test was validated in a general infertility population,[8] as well as in patients undergoing ovarian stimulation with gonadotropins.[9,10] The incidence of abnormal test results increases with age: 3% before age 30, 7% at ages 30 to 34, 10% at ages 30 to 39, and 26% at ages 40 and older. Although an abnormal result on the clomiphene challenge test has a predictive value of 95% to 100% for not achieving pregnancy, the test still has poor sensitivity for identifying patients for whom infertility treatment will not succeed.

In older infertile women, measure FSH on the 3rd day of the cycle

Estradiol

A day-3 estradiol level greater than 80 pg/mL is also associated with a poor response to medical treatment of infertility.

Inhibin

Inhibin is a peptide heterodimer secreted by granulosa cells that inhibits production of FSH. The abnormally high serum levels of FSH seen in infertile women have been attributed to decreased production of inhibin. Although measuring serum inhibin levels may prove to be a better assessment of ovarian reserve, the assay is not available in many centers.

TUBAL DISEASE

Tubal disease, still the most common cause of infertility in the United States, is due in most cases to pelvic inflammatory disease (PID), caused in most cases in the United States by sexually transmitted diseases. Westrom[11] demonstrated 20 years ago that subsequent tubal infertility developed in 12% of women after one episode of PID, in 23% of women after two episodes of PID, and in 54% of women after three episodes of PID.

Hysterosalpingography to assess tubal disease

If the history suggests PID, obtain a sedimentation rate and start doxycycline before a hysterosalpingogram

A hysterosalpingogram will assess tubal morphology and patency. It is usually performed in the follicular phase after the end of the menses. However, if the history suggests PID, a sedimentation rate should be obtained first. If the sedimentation rate is elevated, the hysterosalpingogram should be postponed. If the sedimentation rate is normal, the patient should receive doxycycline 100 mg twice a day for 5 days starting 2 days before the procedure. Patients with dilated tubes on hysterosalpingography are at significant risk of developing an acute pelvic inflammatory disease after the procedure.[12] If dilated tubes are found, doxycycline 100 mg twice a day for 5 days should be given.

Treatment of tubal disease

Patients with evidence of tubal disease should be referred for laparoscopy, as should patients with a documented history of PID.

Mild cases of tubal disease can be treated with laparoscopic surgery. However, in moderate or severe tubal disease, in vitro fertilization produces higher pregnancy rates with a lower incidence of ectopic pregnancy.

ENDOMETRIOSIS

Endometriosis is common and causes significant pelvic pain and infertility.

Endometriosis is characterized by the presence of endometrial glands and stroma outside of the uterus, and reflux of menstrual debris into the peritoneal cavity. However, since most women have some menstrual reflux, there must be an associated immunologic or genetic abnormality that allows endometriosis to develop. Indeed, a variety of cellular and humoral abnormalities have been reported in patients with endometriosis. In particular, the peritoneal cavity has an increased number of activated macrophages, which secrete a variety of cytokines that may be associated with the observed peritoneal inflammatory reaction.

Diagnosis of endometriosis

Deep dyspareunia and dysmenorrhea are the most common symptoms. The peritoneal cavity may have a wide spectrum of lesions ranging from a few peritoneal implants to severe adhesive disease that involves all pelvic organs. Pelvic examination is best carried out during a menstrual period, during which specific areas of tenderness and nodularity can be more easily identified.

There is no blood test or imaging study that can correctly make the diagnosis of endometriosis. Although ultrasonography may identify an ovarian cyst that includes an endometrioma in the differential diagnosis, this finding is not conclusive. All serum markers are nonspecific. At present, laparoscopy is still required to make a definitive diagnosis.

Treatment of endometriosis

Surgery is quite effective in treating advanced endometriosis,[13] although there is some controversy as to its success in early disease. Surgery can usually be done by laparoscopy, especially in the early stages of the disease. Advanced endometriosis with severe adhesive disease can also be treated laparoscopically, but many gynecologists prefer laparotomy,[14] as these cases often have rectal involvement and require extensive pelvic dissection. Pregnancy rates are similar with either approach. Laser surgery has not been shown to be associated

with a higher pregnancy rate than conventional laparoscopic techniques.

If surgery fails or is not an option, then assisted reproductive technology provides an excellent outcome.[15]

Hormonal treatments with drugs that suppress the menstrual cycle, such as gonadotropin-releasing hormone agonists, danazol, or progestins, do not improve fertility in patients with endometriosis.[13]

MALE-FACTOR INFERTILITY

Many cases of infertility are due to problems in the male partner. Among the problems that can lead to decreased sperm counts and other abnormalities and reduced fertility are:

- Environmental toxins
- Drugs (eg, cimetidine, spironolactone, nitrofurans, sulfasalazine, erythromycin, tetracyclines, and anabolic steroids)
- Heavy use of cigarettes, marijuana, or alcohol
- Chemotherapy and radiotherapy for malignancies. (These treatments can severely depress the sperm count, sometimes irreversibly. Patients should be counseled to cryopreserve semen before starting chemotherapy or radiotherapy, as excellent pregnancy rates have been reported with the use of this sperm.[16])
- Increased scrotal temperature due to a febrile illness. This can cause a temporary alteration of semen measures that is only identified 2 to 3 months later—the time required for a germ cell to develop into a mature spermatozoon.

Other conditions that result in an increase in scrotal temperature such as tight underwear have not been shown to alter sperm function.[17]

Semen analysis

The age of the male partner does not affect the ability of the sperm to fertilize an oocyte.[4] However, fertility is compromised with decreasing sperm counts and motility. Normal values proposed by the World Health Organization are given in TABLE 1.

At least two semen analyses should be performed after 2 to 3 days of abstinence. If a test result is abnormal it should be repeated. However if the abnormal result is due to an acute insult such as a viral infection, sperm counts may take 2 to 3 months to return to normal. Therefore the repeat test should be delayed for an appropriate period of time.

TABLE 1

World Health Organization normal values for a semen analysis

MEASURE	NORMAL LIMITS
Volume	2–5 mL
Sperm concentration	≥ 20 million/mL
Motility	≥ 50%
Morphology	≤ 30% abnormal forms
White blood cells	< 1 million/mL

In interpreting semen analyses, it is important that a man not be labeled as infertile if his semen does not does not meet the WHO criteria. Most semen parameters reported on a routine semen analysis have a large coefficient of variation among serial samples from the same man. For example, a recent proficiency testing report by the American Association of Bioanalysts (Brownsville, Texas) reported a coefficient of variation of 20% for sperm count and 39% for morphology. Furthermore, there are many reports of normal fertility with sperm counts as low as 5 million/mL.

If the semen analysis is abnormal, the male partner should be referred for evaluation. Likewise, a history of testicular injury, viral infection, or surgery in a man with an abnormal semen analysis requires a urologic evaluation.

Tight underwear does not decrease sperm function

Treatment of male-factor infertility

The most dramatic change in the treatment of infertile couples in the last decade has been the availability of effective treatment for severe sperm abnormalities.

Intracytoplasmic sperm injection is the direct injection of a single spermatozoon or spermatid into the oocyte. This treatment was introduced in the last 7 to 8 years. Success rates have been equivalent to those of in vitro fertilization cycles with normal sperm. In our

experience, the pregnancy rate per embryo transfer is 41% for patients with normal sperm and 49% for impaired semen.[18] Offspring do not appear to have any developmental problems. There may be a slight increase in sex chromosome abnormalities.

ANOVULATION

Causes of anovulation are:

- Polycystic ovary syndrome (the most common cause)
- Eating disorders
- Competitive exercise
- Stress and anxiety
- Menopause
- Primary pituitary hyperprolactinemia
- Hypothyroidism
- Hyperthyroidism

Evaluation of ovulation

There are several methods of evaluating ovulation.

History. Women with regular monthly periods are unlikely to be anovulatory.

Basal body temperature charts are inexpensive and sometimes useful. However, they are cumbersome and time-consuming. They should not be overinterpreted. If there is a biphasic pattern, the patient is most likely ovulating.

Serum progesterone level. We prefer to measure a single serum progesterone level in the luteal phase. This could be timed on the basis of a home urinary LH test kit. The onset of the LH surge occurs 34 to 36 hours before ovulation. Most LH kits will detect this surge. Urine for LH testing is collected between 10:00 AM and 8:00 PM. It should not be the first urine after waking. In an ideal 28-day cycle, testing for LH is started on the tenth day of the cycle. A serum progesterone level is drawn approximately 5 to 7 days after the LH surge. Levels above 3 ng/mL are indicative of the luteal phase. A serum level above 10 ng/mL is usually associated with an ovulatory cycle with a normal luteal phase.

In PCOS, weight loss and exercise improve insulin resistance and may restore ovulation

Polycystic ovarian syndrome as a cause of anovulation

The most common cause of anovulation in North America is polycystic ovarian syndrome (PCOS)—a metabolic disorder with a primary reproductive manifestation.

The term PCOS is a misnomer: there are no cysts in the classic gynecologic sense. Rather, the ovary has many subcapsular follicles smaller than 10 mm with increased thecal and stromal tissue.

PCOS usually starts at puberty and is associated with irregular periods and some manifestation of hyperandrogenism. Increasing weight influences the expression of the disease. A variety of medical problems are associated with PCOS: dysfunctional uterine bleeding, hyperandrogenic states such as acne and hirsutism, endometrial cancer, lipid disorders, cardiovascular disease, and diabetes mellitus.

Most women with PCOS have insulin resistance that is independent of weight.[19] Fasting and postprandial hyperglycemia are uncommon at the stage of the disease when patients present with infertility, but the patients are at greater risk of developing non–insulin-dependent diabetes at a younger age than the general population.[20] They usually have a strong family history of diabetes or abnormal glucose tolerance. Patients with PCOS who achieve pregnancy often have gestational diabetes. Obesity is an independent disorder with associated endocrine changes that influence the phenotypic expression of PCOS patients.

Insulin resistance appears to have a genetic predisposition and is most likely due to a post-receptor abnormality such as with a glucose transporter rather than a receptor defect. Insulin can directly influence enzymes that are involved in androgen steroidogenesis as well as decreasing sex hormone-binding globulin.

Diagnosis of PCOS. This syndrome is diagnosed if there is a history of a menstrual disorder such as amenorrhea or oligomenorrhea associated with androgen excess. The androgen excess could have a clinical manifestation such as hirsutism or acne, or be found on laboratory testing (TABLE 2). Serum androgen levels are usually in the upper range of normal or higher.

Other disorders that may cause a similar picture are 21-hydroxylase deficiency, Cushing syndrome, and an androgen-secreting

adrenal or ovarian tumor.

Patients usually present with a menstrual disorder or an infertility problem caused by anovulation. Serum levels of testosterone and 17-hydroxy progesterone should be measured. If the patient has a history of irregular menstrual periods, then serum levels of TSH, prolactin, FSH, and LH should also be measured. If the patient presents with amenorrhea, then serum estradiol levels should also be assessed.

The evaluation of a patient with PCOS should include a simple measure of insulin resistance. We recommend measuring fasting serum levels of glucose and insulin. A ratio of glucose to insulin of less than 4.5 is consistent with insulin resistance.[21] Long-term monitoring for abnormal glucose levels is necessary.

Treatment of PCOS should focus on modifying insulin resistance. The primary approach is diet, weight loss, and exercise.[22] In one study,[23] 60 of 67 anovulatory patients with a body mass index of 30 kg/m^2 or more resumed spontaneous ovulation after losing 10 kg. Seventy-seven percent of these patients achieved pregnancy, either spontaneously (35%) or with the help of medication. The miscarriage rate was significantly reduced.

If diet and exercise are not successful, clomiphene citrate can be given to induce ovulation. This drug is started at 50 mg/day from cycle days 5 through 9. If ovulation is not detected, the dose is increased in subsequent cycles in increments of 50 mg to a maximum dose of 200 mg.

If maximal doses of clomiphene do not induce ovulation, additional medication can be given. Metformin (Glucophage) or troglitazone (recently withdrawn from the market) can decrease insulin levels, decrease androgen levels, and result in ovulatory cycles.[24] The dosage of metformin is 500 mg three times per day.

Low-dose corticosteroids with clomiphene may help if the adrenal androgens are elevated. If ovulation is still not induced, the patient should be referred for ovulation induction with gonadotropins. These patients have a high rate of ovarian hyperstimulation syndrome.

TABLE 2

Clinical and biochemical manifestations of polycystic ovary syndrome (PCOS)*

Clinical
- Infertility
- Menstrual disorder
- Obesity
- Androgen excess
- Acanthosis nigricans

Biochemical
- Elevated serum androgens
  - Testosterone
  - Androstenedione
  - Dihydroepiandrosterone (DHEA)
- Decreased sex hormone-binding globulin
- Insulin resistance (fasting glucose/insulin ratio > 4.5)
- Abnormal LH/FSH ratio (≥ 2)
- Abnormal lipoprotein profile
  - Increased triglycerides
  - Increased low-density lipoprotein cholesterol and total cholesterol
  - Decreased high-density lipoprotein cholesterol
- Mildly elevated prolactin

Imaging studies
- Ultrasonographic appearance of polycystic ovary syndrome

*Not all the manifestations are present in all patients

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