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Infertility: A practical framework

ABSTRACT

Fertility concerns are common in men and women of reproductive age, and primary care physicians are often the first line in addressing, assessing, and referring these patients. This article reviews the answers to questions patients often ask, and outlines a practical framework for the evaluation and management of the infertile couple. Up-to-date information is provided on available assisted reproductive technologies for the infertile couple, as well as preserving fertility in the setting of aging-related changes in the female reproductive system.

KEY POINTS

A primary care physician can provide advice and testing regarding most fertility concerns.

Female reproductive aging is a central threat to fertility, and prompt assessment and referral are warranted for women age 35 and older.

Male factor infertility can now often be overcome with assisted reproductive technologies.

Polycystic ovary syndrome can cause anovulation and has metabolic effects that can evolve into metabolic syndrome, with serious health consequences.

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For millions of couples, a primary care physician may be the first point of contact for fertility concerns. Statistics from the US Centers for Disease Control and Prevention indicate that 12% of women ages 15 to 44 received fertility services from 2006 to 2010.[1] Despite seeking services, most couples requested only advice or testing rather than treatments such as ovulation-inducing medications, surgery, or, rarely, assisted reproductive technologies including in vitro fertilization. Based on these data, primary care physicians are in a unique position to offer guidance and provide fertility services in most circumstances without the need for referral.

This article reviews the answers to questions patients frequently ask, and outlines a practical framework for the evaluation and management of the infertile couple.

MANY PATIENTS SEEK INFORMATION

At least 1 million medical visits per year are for women seeking help in becoming pregnant, with the number increasing over the last several decades.[1] Reasons for the increase include delayed childbearing and the effects of aging on the female reproductive system ("female reproductive aging"), as well as the availability of increasingly effective treatments for infertility.

While the prevalence of infertility in US couples is widely quoted as 10% to 15%,[2] there is no estimate for the number of fertility-related questions patients routinely pose to care providers. These questions often relate to coital timing, use of lubricants, positioning, and the use of fertility trackers and ovulation predictors.

TABLE 1

Common causes of infertility

Pelvic disease (tubal disease, fibroids, endometriosis)
Male factor
Disorders of ovulation
Female reproductive aging
Idiopathic

A 2017 study of women with 12 months of infertility found that only 8% sought subspecialist care vs care from a general physician or provider, indicating that generalists are most often the first point of contact.[3] The majority (92%) of women responding to a survey regarding fertility-awareness education indicated a preference for immediate counseling from their general practitioner.[4]

Although some healthcare providers may consider infertility simply a quality-of-life issue, the World Health Organization classifies it as a disease, and as such it warrants identification, assessment, and intervention.[5] Further, patients with infertility are known to experience considerable psychological distress related to their condition. In a comparison study, women with infertility experienced levels of psychological distress similar to the level in patients with cancer and patients with chronic medical illness.[6]

Primary care physicians can counsel, evaluate, and treat many common fertility problems

In the current era, general practitioners and women's health specialists may also now address patients' questions about reproductive aging and egg-freezing, which is now an established technology.[7]

FAILURE TO CONCEIVE AFTER 1 YEAR

The American Society of Reproductive Medicine (ASRM) defines infertility as failure to conceive after 1 year of appropriately timed unprotected intercourse[8]; 85% of couples will have achieved a pregnancy within this time period.[9] In practice, some women are evaluated sooner if they are of advanced maternal age (> age 35) or report a history of chemotherapy or radiation exposure, anovulation, or risk factors for obstructed fallopian tubes (ie, endometriosis, fibroids, or pelvic inflammatory disease). Common causes of infertility are listed in **Table 1**.

As women approach age 40, the potential for fertility decreases rapidly and significantly. Women in their later 30s have only half the fertility of women in their early 20s.[10] Misperceptions of aging and female fertility have been fueled by widely publicized celebrity births from women in their 40s and even 50s, without disclosing the use of frozen or donor eggs. This unfortunate fact affects women actively trying to conceive as well as women who wish to delay childbearing due to lack of a partner or for personal or professional reasons. Primary care physicians should be able to provide counseling relevant to female reproductive aging and make suitable and timely referrals for fertility preservation if indicated.

AN EMOTIONAL ISSUE

In approaching the couple with infertility, it is important to proceed with great sensitivity for the socioemotional context of this diagnosis. For both the male and female partner, infertility can be highly stigmatizing, and can be viewed as a personal or relationship failure.

Couples should be encouraged to ask embarrassing or uncomfortable questions. Although this may not be feasible in many circumstances, interviews should ideally be conducted with both partners individually as well as together, to allow sensitive issues to be shared. In some cases, a partner may be unaware of a history of a sexually transmitted infection, a prior abortion, the use of testosterone supplements or medications to enhance male sexual performance, or a vasectomy or tubal ligation during a previous relationship.

It is not unusual that the anxiety of infertility can cause decreased libido and sexual and erectile dysfunction. These issues can further complicate the problem of conceiving, and couples counseling is not uncommonly required.[11] Patients are often reassured to know that they are not alone in their diagnosis.

LOOK FOR CLUES

Before embarking on a series of tests, the primary care physician can carefully evaluate for clues that may guide the diagnostic evaluation. The approach can be individualized based on

the patient's age, duration of subfertility (ie, how long they have been trying to become pregnant), and risk factors. But as a general rule, regardless of age, couples who have been trying to conceive for more than 1 year should be encouraged to pursue additional testing.

Because each month presents a new cycle of hope (often followed by intense disappointment), the prevailing sentiment to "just give it a little more time" must be countered by education and counseling. The primary care physician must increase awareness that lack of pregnancy in the stated time periods is a compelling reason for evaluation.

History-taking in the infertile couple should include a complete gynecologic and menstrual history. A history of sexually transmitted diseases that can cause tubal disease, such as gonorrhea and *Chlamydia*, is significant. Both partners should be assessed for a history of prior conceptions, past medical or surgical problems, medications, and exposures to environmental toxins including alcohol, tobacco, and drugs.

A detailed physical examination can provide clues to the cause of subfertility, especially if signs of obesity, androgen excess, or insulin resistance are present.

QUESTIONS OFTEN ASKED BY COUPLES TRYING TO CONCEIVE

Clinicians are frequently asked questions related to sexual practices and lifestyle in relation to fertility and should be comfortable responding to questions in these areas.

Does frequent ejaculation 'use up' my sperm?

Men should be reassured that frequent ejaculations do not decrease sperm counts; even daily ejaculation does not deplete the concentration of sperm. Male partners can be reassured that "saving up" is not an effective strategy; in fact, abstinence periods of greater than 5 days can adversely affect semen parameters.[12]

How often should we have sex?

Infrequent intercourse (< 1 time per week) reduces the monthly chance of conceiving.[13] There does not seem to be a significant improvement in fecundity with daily intercourse vs intercourse on alternate days. Strict schedules surrounding intercourse may increase stress, and reassurance should be offered that intercourse need not be regimented. Every 1 to 2 days should suffice.

Are any sexual positions better for conception?

There is no evidence that particular coital positioning or remaining supine after intercourse improves fertility. Sperm can be found within the endocervix within seconds of ejaculation, irrespective of sexual position.

What is the window of fertility?

There is good evidence that the fertile window lasts approximately 6 days and closes after ovulation.[13,14] Women with regular cycles can determine their typical day of ovulation based on menstrual tracking. Intercourse should begin about 6 days before ovulation and should continue every 1 to 2 days for 1 week to fully capture this window.

Should we change our lifestyle?

Couples seeking pregnancy should be advised to limit alcohol and caffeine use, completely abstain from cigarette smoking or illicit drug use, and maintain a healthy body mass index.

Very few data exist to support particular diets or supplements to promote fertility, including antioxidants and herbal remedies. Folic acid supplementation is recommended in all women attempting to conceive to reduce the incidence of birth defects.

Look for indications for prompt referral such as pelvic pathology or male factor infertility

Do lubricants reduce fertility?

Although there seem to be no differences in fecundity rates in couples using commercial lubricants, most water-based lubricants are best avoided in couples with infertility, as adverse effects on sperm have been demonstrated in vitro.[15] If lubrication is needed, couples may try mineral oil, canola oil, or hydroxyethylcellulose-based lubricants (eg, Pre-seed).

Do fertility trackers work?

Many couples with primary infertility perceive that coital timing is critical and worry that their infertility is due to poorly timed intercourse; in fact, this is seldom the case.

Despite widespread marketing of urinary luteinizing hormone (LH) detection kits and electronic trackers and monitors, there is no clear evidence that these methods improve

TABLE 2

Fertility tests that are no longer used in clinical practice

Postcoital testing
Routine laparoscopy or hysteroscopy for unexplained infertility
Endometrial biopsy for endometrial dating
Prolactin, unless in cases of anovulation or oligo-ovulation
Advanced sperm function testing
Thrombophilia or immunologic testing
Parental karyotyping

monthly rates of conception.

Women with a regular menstrual cycle should be encouraged to take notice when their cervical mucus appears clear and slippery (a sign of ovulation). Not all women are able to detect these fluctuations; however, for those who can, observing cervical mucus changes appears to be equivalent or superior to predictor kits in predicting conception.[16]

A PRACTICAL FRAMEWORK FOR EVALUATING THE INFERTILE COUPLE

Overlooking a coexisting diagnosis may lead to delays in treatment and pregnancy

To assess for the common factors identified in **Table 1**, the essential investigation of the infertile couple includes:

- Semen analysis
- Confirmation of ovulation
- Hysterosalpingography.

Consideration can also be given to ovarian reserve testing in women at risk of diminished ovarian reserve. The above investigation can be performed simultaneously to allow for prompt identification of any issues. Further, infertility is often a combination of problems (eg, anovulation in the woman together with a problem in the man), so an incomplete evaluation may overlook a coexisting diagnosis and lead to delays in treatment and pregnancy.

Although abnormal results from this screening will likely prompt referral to a fertility specialist, most patients seeking management from their primary care physician simply want assessment and education.

Tests that are no longer typically used in clinical practice are outlined in **Table 2**.

OVARIAN RESERVE TESTING AND FEMALE REPRODUCTIVE AGING

Ovarian reserve refers to the number of fertilizable oocytes that remain in the ovary. This reserve changes over time, and changes occur rapidly as women approach and enter their 30s. Though not the case in men, the age of the female partner is an independent risk factor for infertility. This discrepancy is due to loss of ovarian reserve, chromosome abnormalities in embryos, and the development of medical conditions with age that affect fertility.

Testing for ovarian reserve does not necessarily predict an overall inability to achieve a live birth,[17] but it can predict response to exogenous gonadotropins and, to some degree, the chance for successful pregnancy with assisted reproductive technology.[18]

The ASRM states that testing for diminished ovarian reserve may provide useful information in women who have had a previous poor response to gonadotropins and in women planning assisted reproductive technology.[19] The ASRM also indicates that the following are risk factors for diminished ovarian reserve, and clinicians may target the assessment accordingly[19]:

- Age 35 or older
- History of exposure to chemotherapy or pelvic radiation
- Family history of early menopause (age < 40)
- History of ovarian surgery
- Unexplained or idiopathic fertility.

Although several tests of ovarian reserve exist, either an antimullerian hormone (AMH) test or a combined cycle day-3 follicle-stimulating hormone (FSH) and estradiol level are the 2 tests commonly used in clinical practice. Antral follicle counts are an ultrasonographic measure used by infertility specialists but rarely by primary care physicians. Assays such as inhibin are rarely ordered and have limited clinical utility.

The AMH test

Many reproductive endocrinologists rely on the AMH level as a single test of ovarian reserve as it is easy to obtain, has a relatively low cost, and offers stable results. AMH is produced by the granulosa cells of the ovarian

antral follicles and is readily detected in serum samples.

Conveniently for the clinician, levels of this hormone remain stable throughout the menstrual cycle and therefore can be tested on any day and at any time of day. Lower serum AMH levels (< 1 ng/mL) have been shown to correspond to diminished ovarian stimulation with gonadotropins as well as decreased embryo quality and poor pregnancy outcomes with assisted reproductive technology.[19]

Nevertheless, despite overall stability, AMH levels can be falsely lowered in women using exogenous hormones or with a diagnosis of hypogonadotropic hypogonadism. Levels may be higher than expected in women with polycystic ovary syndrome due to higher numbers of antral and preantral follicles in the polycystic ovary.

The day-3 follicle-stimulating hormone test

FSH and 17-beta estradiol testing can be ordered in combination to assess function of the hypothalamic-pituitary-ovarian axis on day 3 of the menstrual cycle. There is some flexibility, however, and testing obtained on cycle day 2, 3, or 4 yields equivalent results.

Although there are no strict cutoffs, FSH levels that appear elevated (> 10–20 IU/L) are associated with lower chances of conceiving with in vitro fertilization in multiple studies.[20]

The test is limited by levels that may fluctuate cycle to cycle, and reassuring test results do not necessarily indicate that a woman will achieve a pregnancy. Although a serum estradiol value alone is not a useful test, it can be used in combination with day-3 FSH to screen for diminished ovarian reserve.

As premature recruitment of a follicle can cause an early follicular rise in estradiol, FSH may be falsely suppressed on day 3. For example, a "normal" day-3 FSH combined with an elevated day-3 17-beta estradiol level of 60 to 80 pg/mL is associated with a poor response to medical treatments for infertility.

Female reproductive aging

Aging of the female reproductive system is a central threat to fertility, and prompt assessment and referral are warranted for women age 35 or older who have been trying to conceive for more than 6 months. The ASRM recommends that women over age 40 be evaluated immediately.[21]

A prevailing misconception is that regular menstrual cycles correspond with normal fertility. In reality, women lose their ability to achieve a healthy live birth in the 5 to 10 years preceding menopause. Although all women who do not desire pregnancy should still use appropriate contraception to avoid unintended pregnancy, women who do desire pregnancy should be aware of these physiologic changes.

Classic age-related changes in ovarian reserve are accompanied by a steep rise in aneuploidy and miscarriage risk.[22] This is particularly relevant as women increasingly delay childbearing in modern society. Loss of fertility begins at 32 and abruptly accelerates at age 37[21]; this fact is poorly communicated to and understood by patients. In a 2018 study of highly educated women, most respondents failed to identify that 45-year-old women can only rarely achieve a successful pregnancy.[23]

In recent decades, the percentage of women who delay childbearing until after age 35 has steadily increased. There is a widespread misconception that fertility treatments and assisted reproductive technology can compensate for female reproductive aging. Primary care physicians can play a central role in reminding couples that age remains the single greatest predictor of natural fertility and the chance of success with assisted reproduction.

In women, loss of fertility begins at 32 and abruptly accelerates at age 37

Further, for women who desire future fertility and are without a partner, primary care physicians can counsel them regarding the availability of donor insemination or egg freezing. Studies confirm that women want clinicians to initiate information on reproductive health, and 80% of women undergoing elective egg-freezing for fertility preservation wished that they had done so at an earlier age.[24,25]

FEMALE PERITONEAL AND STRUCTURAL CAUSES

Women with endometriosis, fibroids, or a history of tubal disease have impaired fecundity. Pelvic imaging is an essential component of their evaluation. Although hysterosalpingography is the mainstay of tubal assessment, in select cases ultrasonography or hysteroscopy may be indicated.

Tubal disease and hysterosalpingography

Tubal disease remains one of the most common causes of infertility in the US females. In most cases, tubal damage is secondary to pelvic inflammatory disease from infection with gonorrhea or *Chlamydia*, or both.

Rates of confirmed tubal-factor infertility have been shown to increase with both the severity of the infection and the number of past infections.[26] In a landmark study, 1 episode of pelvic inflammatory disease was associated with a 12% risk of tubal-factor infertility, whereas 3 infections carried a risk as high as 54%. Pelvic inflammatory disease is also known to increase the risk of ectopic pregnancy.

To assess tubal patency, hysterosalpingography, a radiographic procedure, is typically performed using fluoroscopy and injected contrast material. Some centers may offer sonohysterography as a radiation-free alternative, depending on sonographic skill and experience. Both tests are best scheduled in the window between the end of menstrual bleeding and ovulation. In practice, patients with regular cycles can typically schedule hysterosalpingography between cycle days 5 and 12.

In most cases, tubal damage is secondary to pelvic inflammatory disease from infection with gonorrhea or *Chlamydia*, or both

In patients with known hydrosalpinx (a distended fallopian tube due to blockage) or a history of pelvic infection, doxycycline should be given before the procedure.[27] Patients with demonstrated hydrosalpinx on hysterosalpingography should receive doxycycline 100 mg twice daily for 5 days to prevent posthysterosalpingography pelvic inflammatory disease.[27] Patients with active pelvic or cervical infection should not undergo hysterosalpingography .

Women with confirmed hydrosalpinx or tubal obstruction can be referred for laparoscopy. Gynecologic surgeons will plan their approach based on whether the obstruction is proximal (near the uterus) or distal (near the ovary) as well as whether hydrosalpinx, abnormal tubal architecture, salpingitis isthmica nodosa, or peritubal adhesions are noted. Tubal surgery can be effective in mild cases of tubal disease; however, as in vitro fertilization is becoming more effective, patients with moderate or severe tubal disease are increasingly being referred directly for assisted reproductive technology. Before undergoing assisted reproductive technology, hydrosalpinx will need to be addressed, as it can decrease clinical pregnancy rates with in vitro fertilization.

Endometriosis

Endometriosis is found in 21% to 47% of women with subfertility[28] and commonly causes pain, ovarian cysts, and tubal disease. There is often a delay of 7 to 8 years for diagnosis due to the misapprehension that severe dysmenorrhea is normal. Women with an affected first-degree family member are at substantially increased risk.

Although endometriosis is commonly thought to result from reflux of endometrial tissue into the peritoneal cavity with menses, there are multiple proposed mechanisms for the disease.[29] The pathogenesis of endometriosis is enigmatic, and there are likely as yet undetermined immunologic and genetic predispositions that confer increased risk.

Common symptoms of endometriosis are dysmenorrhea, dyspareunia, and pelvic pain, and these are sometimes accompanied by bowel and bladder symptoms. Pelvic examination classically demonstrates an immobile uterus and uterosacral nodularity; palpation of these nodules can elicit pain. On laparoscopy, endometriosis can range from minimal to severe; however, stage of endometriosis correlates poorly with reported symptoms.[30]

Consideration of surgery is based on clinical history, results of the pelvic examination, and possible findings on ultrasonography or hysterosalpingography. Although positive findings on imaging can support a plan for intervention, endometriosis is largely a peritoneal disease, and evidence of tubal damage or ovarian cysts is rarely evident on ultrasonography. In women with menstrual complaints (eg, dysmenorrhea, heavy menstrual bleeding, abnormal uterine bleeding) and a history of infertility, ultrasonography may be useful in determining the presence of uterine pathology such as ovarian cyst or endometrioma, large hydrosalpinx, polyp, or substantial fibroid burden—any of which may have a significant impact on female fertility.

In the absence of a reliable blood test or imaging study, the gold standard for the diagnosis of endometriosis continues to be laparoscopic surgery. Hormonal treatments for endometrio-

sis symptoms are not effective in improving infertility and will preclude pregnancy. Laparoscopic surgery is more successful in improving pregnancy rates in women with advanced disease: pregnancy rates after surgery can be as high as 60% in women with ovarian endometriomas but are significantly lower in women with removal of minimal to mild disease.[30,31] Women over age 35 or who present with low ovarian reserve and whose male partner has semen abnormalities should consider moving directly to assisted reproductive technology rather than pursuing endometriosis surgery.

MALE FACTOR INFERTILITY

Although male partners are often highly engaged in and supportive of the fertility evaluation, some are reluctant to undergo testing, and some wish to undergo semen analysis only after female factors have been ruled out. Our practice is to evaluate male factors immediately, due to the high contribution of male factors (up to 40% of cases) either alone or in combination with female factors.[32]

Men at particularly increased risk of semen abnormalities include those with a history of chemotherapy or radiation or exposure to toxins (eg, environmental exposures, alcohol, tobacco, illicit substances) and prescribed medications.

At a minimum, for the male partner, a reproductive history should be taken and a semen analysis ordered. Men should be directly queried about testosterone use, as this often-used anabolic steroid hormone can severely impair sperm production.

Normal semen parameters as designated by the World Health Organization[33] are listed in **Table 3**. Home collection can be offered at some centers to allay any uneasiness associated with the procedure. Although frequent ejaculation does not appear to affect sperm counts, the ASRM recommends performing formal semen analysis after a window of abstinence of 2 to 5 days.[34] The test should be repeated if the result is abnormal, as transient influences such as recent illness may manifest in the sperm parameters for up to 3 months after recovery; this extended effect is related to the duration of normal germ cell maturation. Although there are some differences in sperm parameters of older men, reproductive success does not seem significantly diminished.

TABLE 3

World Health Organization reference values for semen analysis, 2010

Parameter	Lower reference value
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15 million/mL
Total sperm number	39 million sperm per ejaculate
Percent motility	40%
Forward progression	32%
Sperm morphology (% normal forms by Kruger strict criteria)	4%

Information from reference 33.

Men who have low sperm counts, motility, or morphology scores based on World Health Organization criteria should not be deemed "infertile," as there is significant variation from one analysis to the next, and normal fertility has been reported in men with notably low sperm counts. Particular caution should be exercised in interpreting low morphology scores in men with normal counts and motility, as this parameter appears to have the least prognostic value in this context. Men with abnormal semen analyses should be referred to a specialist for further urologic evaluation and treatment.

Treatments for male factor infertility include surgery, steroid hormones, and possibly intrauterine insemination or assisted reproductive technology. In even the most challenging cases, male infertility is now largely treatable with intracytoplasmic sperm injection with assisted reproductive technology. While most advances in in vitro fertilization have been evolutionary, intracytoplasmic sperm injection was revolutionary. This breakthrough technology allows a single sperm to be injected directly into the oocyte. Sperm for this procedure can be obtained either from the ejaculate or from microsurgical testicular sperm extraction.

Most advances in in vitro fertilization have been evolutionary, but intracytoplasmic sperm injection was revolutionary

ANOVULATION

Anovulation manifests with oligo- or amenorrhea and may explain up to 40% of female

TABLE 4

Common causes of anovulation

Polycystic ovary syndrome
Hypothalamic amenorrhea due to extreme nutritional, emotional, or physical stressors
Menopause
Hyperprolactinemia
Thyroid disease (hyperthyroidism, hypothyroidism)

infertility.[2] There are myriad causes of anovulation (**Table 4**); however, polycystic ovary syndrome is the most common.

A thorough menstrual history can be informative, as most females of reproductive age have a fairly predictable 25-to-35-day monthly menstrual cycle. Women presenting with menstrual charting with this pattern do not require laboratory confirmation of ovulation. Basal body temperatures are rarely used currently, as they are time-consuming, can induce stress, and are confirmatory rather than predictive of ovulation. Endometrial biopsy for endometrial "dating" is no longer performed in infertile women.

If laboratory confirmation is desired, LH kit testing with a commercially available test or a luteal phase serum progesterone obtained 7 days after suspected ovulation can be obtained. A serum progesterone level higher than 3 ng/mL is indicative of ovulation.[19] Due to the notable fluctuations in ovulatory-appearing progesterone levels over several hours, caution must be taken in interpreting a lower-normal level as indicative of a luteal phase insufficiency.

Despite the name, polycystic ovary syndrome does not involve classic ovarian cysts

Polycystic ovary syndrome

Polycystic ovary syndrome is important to understand because it is a metabolic condition that predisposes patients to a variety of health risks. Along with gynecologic consequences such as infertility, abnormal uterine bleeding, and endometrial pathology, it is often accompanied by alterations in glucose and lipid metabolism, obesity, hypertension, and cardiovascular disease.[35]

Despite its name, the syndrome does not involve the presence of classic ovarian cysts. In fact, the cysts associated with polycystic ovary syndrome are dense accumulations of antral follicles arranged peripherally in the ovarian cortex; they should not be removed surgically as they represent the ovarian reserve.

Although ovaries that appear polycystic on transvaginal ultrasonography are often associated with the syndrome, they are not invariably present and are not absolutely required for the diagnosis of polycystic ovary syndrome based on the most commonly used criteria.[35] Several diagnostic criteria have been proposed for polycystic ovary syndrome and its phenotypes. The 2003 revised Rotterdam criteria require 2 out of the following 3 features:

- Oligo-ovulation or anovulation
- Evidence of hyperandrogenism, whether clinical (eg, acne or hirsutism) or based on laboratory testing
- Polycystic-appearing ovaries on ultrasonography.

There is no single test that can diagnose the disease. Although polycystic ovary syndrome is often characterized by elevated LH levels, LH–FSH ratios, and fasting insulin levels, these are not diagnostic criteria. The diagnosis hinges on excluding other causes of anovulation such as thyroid disease, hyperprolactinemia, 21-hydroxylase deficiency, androgen-producing neoplasms, and Cushing syndrome. In addition to checking serum testosterone levels, irregular menstrual cycles and infertility should be assessed at minimum with measurement of TSH, prolactin, and day-3 FSH. Obese women should be screened for metabolic syndrome, which should include an assessment of impaired glucose tolerance with a 2-hour oral glucose tolerance test.[36]

Women with polycystic ovary syndrome are known to have insulin resistance, which is difficult to assess and is independent of their body mass index.[37] They often report a family history of diabetes or a personal history of gestational diabetes or giving birth to infants who are large for gestational age. Although most women diagnosed with insulin resistance and anovulatory infertility will not yet have a diagnosis of diabetes, women with polycystic ovary syndrome are 3 to 7 times more likely to develop type 2 diabetes later in life[37] and are at increased risk of lipid abnormalities, cardiovascular disease, and stroke. Therefore,

interventions to address the compounding influences of polycystic ovary syndrome and obesity can improve fertility outcomes and help prevent long-term sequelae that accompany the syndrome.

Treatment for women with polycystic ovary syndrome attempting conception includes lifestyle modifications, medications for ovulation induction, and possible use of insulin sensitizers. Metformin alone is not effective as a single agent for achieving pregnancy.[38] Diet, weight loss, and exercise can have dramatic effects on ovulation and pregnancy and should be highly encouraged.

Ovulation induction is often required in anovulatory women, either in combination with lifestyle modifications or used subsequently if modifications are not successful. Letrozole is advised as the initial agent in women with obesity and anovulatory infertility rather than clomiphene citrate; a side-by-side comparison demonstrated increased rates of ovulation and live birth with letrozole.[39]

Once-daily letrozole 2.5 mg or clomiphene 50 mg can be prescribed for 5 days, from cycle days 3 through 7 to cycle days 5 through 9. If this initial dosing fails to result in ovulation, the dose can be increased. Known adverse effects are hot flashes, headaches, ovarian cysts, and increased risk of multiple gestation.

Metformin should be considered as an adjunct to fertility treatments in women with polycystic ovary syndrome, especially those with obesity or impaired glucose tolerance, or if there is no response to standard ovulation induction.

Ovarian hyperstimulation syndrome (cystic enlargement of the ovaries with potentially dangerous fluid and electrolyte imbalances) can occur in women with polycystic ovary syndrome; however, it rarely occurs with oral medications.

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