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Infertility: Help for couples starts with you

A patient tells you she's "starting to worry" that getting pregnant won't be as easy as she'd hoped. Before you provide a referral, look for clues in the couple's histories.

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PRACTICE RECOMMENDATIONS

› *Evaluate the fallopian tubes and their patency when menstruation is normal. Also, consider arranging for a hysterosalpingogram.* (B)

› *Suspect polycystic ovarian syndrome when adiposity, acne, and hirsutism with menstrual irregularity are factors.* (B)

› *Suspect androgen deficiency when a man's arm span is >2 cm longer than his height, or when he has experienced a loss of pubic, axillary, or facial hair.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

During an annual visit, a patient confides in you that she and her husband have been trying to get pregnant for a year, but haven't had any success. She tells you that she's starting to get worried.

How do you advise her? What are your next steps?

The approach to evaluating infertility complaints is usually straightforward and can lead to a positive outcome. Not surprisingly, the dialogue often begins with you, the family physician. Your attention to clues in each partner's history can do much to get to the heart of the problem. And even if a couple requires a specialty referral, it's best to be familiar with the more extensive evaluation and management options they'll encounter to help them anticipate likely discussions in their consultations. In this article, we review the best evidence for the care of your patients who want to conceive.

Who's affected?

Infertility difficulties may be attributable to one or both partners, may be multifactorial, or may be unexplained (**TABLE**).

In women, *infertility* is the inability to conceive after 1 year of unprotected regular intercourse in those younger than 35 years, and after 6 months in those 35 years and older.[1] *Fecundability* is the probability of achieving pregnancy in 1 menstrual cycle. Normal fecundability with a single menstrual cycle is ~20%, peaking between the ages of 20 and 24 years.[2] Fecundability decreases slightly at age 32 and declines progressively and more rapidly after age 40. Spontaneous miscarriage is a factor; its rate in younger women is ~10% and in women >40 years is ~40%.[2] Overall, approximately 13% of women between the ages of 15 and 44 have fecundity impairment, with more than 6 million women in the United States affected.[2]

About 24% of all cases of infertility are due to male factors—seminiferous dysfunction, including problems with

TABLE

Consider these factors in cases of suspected infertility[3,6,21,23,40,41]

Major causes of infertility		Infertility risk factors
Female		
Cause	**Contribution**	• Advanced endometriosis • Autoimmune disease • Exposure to cytotoxic drugs or radiation therapy • Family history of premature ovarian failure or menopause • Inability to conceive with past partners • Previous ovarian surgery • Smoking • Suspected uterine or tubal disease
Endocrine factors	45%-55%	
PCOS Thyroid Diabetes mellitus Prolactinemia	21%-28% 10%-20% 10%-20% 7%	
Tubal and peritoneal pathology	30%-40%	
Ovulatory dysfunction*	15%	
Cervical and uterine factors	<5%	
Male		
Cause	**Contribution**	• Adult mumps • Chemotherapy and/or radiation • Drug use • History of testicular trauma • Erectile or sexual dysfunction • Inability to conceive with past partners • STIs • GU infections • History of surgical procedures to inguinal and/or scrotal area
Seminiferous tubule dysfunction	60%-80%	
Posttesticular defects	10%-20%	
Primary hypogonadism	10%-15%	
Hypothalamic pituitary disease	1%-2%	

*Assuming appropriate ovarian reserve, indicated by follicle-stimulating hormone (FSH) level <10 mIU/mL, FSH-to-luteinizing hormone ratio <2, and estradiol level <50 pg/mL.

GU, genitourinary; PCOS, polycystic ovarian syndrome; STIs, sexually transmitted infections.

motility, morphology, and volume of sperm; primary hypogonadism; posttesticular defects; and hypothalamic pituitary disease.[3] Recent observational trends show declines in fertility among men older than 40, and among men from different areas in the country, thus raising the issue of the role that environmental pollutants or toxins may play. Supposed increases in urogenital abnormalities and testicular cancers may also contribute to declining fertility rates.[4,5]

Zero in on these areas of the history

As with any diagnostic work-up, the most important aspect of an infertility evaluation is the history. Document menstrual cycle length and regularity and the timing of intercourse. (Ideally, this would be done when a couple first decides to conceive.) It's important to know how long the couple has been trying to become pregnant. More time may be all they need to achieve pregnancy. Educate them on reproductive cycles and optimal timing to achieve pregnancy. Some women experience lower abdominal pain (mittelschmerz) signifying release of an egg from the ovary, which can help identify the time of ovulation.

Remember, too, the role that a couple's psychological state can play; worries over suspected infertility may cause anxiety, anger, depression, and marital troubles.

Is it her?

Regular menstrual cycles—menses occurring every 21 to 35 days—carry an ovulation probability of 95% with each cycle.[6] With normal menses, ovulatory dysfunction is an unlikely cause of infertility. If menstrual cycles are irregular, ovulatory function is not normal

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and cyclical. Explore the woman's medical, surgical, and gynecologic histories, looking particularly for thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, dysmenorrhea, dyspareunia, pelvic inflammatory disease (PID), and abdominal or pelvic surgery.

The fallopian tubes. When menstruation is normal, evaluate the fallopian tubes and their patency; 30% to 40% of infertility cases can be related to peritoneal pathology.[3,7] Inability to conceive in a previous relationship, history of PID, or prior tubal surgery all correlate to infertility. Ten percent of patients with a history of one PID episode and 54% to 75% of patients with 3 episodes will have patency issues.[7]

Consider arranging for a hysterosalpingogram (HSG) in all patients as part of an initial work-up for infertility.[8] HSG is useful in evaluating tubal patency and the uterine cavity, and it can be therapeutic. HSG is not useful in detecting peritubal adhesions or endometriosis; patients in whom you suspect these conditions should undergo diagnostic laparoscopy. If abnormalities are found on HSG, refer patients to a reproductive endocrinologist to evaluate treatment options.

Chlamydia trachomatis IgG antibody testing can predict the presence of tubal disease. For women with low risk of tubal disease, it may be more cost effective to test for the *Chlamydia* antibody and proceed with HSG if the result is positive. Antibody testing is also useful for women with an allergy to contrast dye who cannot undergo an HSG. If the antibody test result is positive, consider arranging for a sonohysterogram to evaluate for the presence of fluid in the cul-de-sac, or an intrauterine infusion of saline to evaluate the patency of at least one tube.[9]

Ovulatory function. To assess ovulatory function, measure a midluteal-phase serum progesterone level, drawn 1 week before the expected day of menses (Day 21 of a 28-day cycle). A level >3 ng/mL is evidence of ovulation. Over-the-counter ovulation kits detect the luteinizing hormone (LH) surge but have false-positive and false-negative rates of 5% to 10%, respectively.[10] Recording basal body temperature is a noninvasive and inexpensive means of evaluating ovulation. The patient must record temperatures at exactly the same time each day. Have her log the temperatures and watch for a spike that occurs 1 to 2 days after the LH surge. The average woman's temperature rises above 98°F in progressing from the follicular to the luteal phase. Since the spike occurs 1 to 2 days after ovulation, this method is best used for many months so the woman can predict her cycle.[11]

Once timing of ovulation has been established, you can check lab results at Day 3 of the woman's cycle for follicle-stimulating hormone (FSH), LH, estradiol, thyroid-stimulating hormone (TSH), prolactin, and 2-hour fasting glucose tolerance. In addition to polycystic ovarian syndrome (PCOS), patients may have ovulatory dysfunction secondary to glucose intolerance.

A clomiphene (Clomid) challenge can help in assessing ovarian reserve. Administer 100 mg clomiphene on Days 5 through 9 of the patient's cycle, and check FSH and estradiol levels on Day 10. With diminished ovarian reserve, FSH will increase to >12 mIU/mL and estradiol to >300 pg/mL.[12] If this occurs, consider referring for an ultrasound measurement of antral follicle count. The presence of 4 to 10 follicles measuring 2 to 10 mm in diameter suggests adequate reserve.[13]

Although not widely available in the United States, the test for antimüllerian hormone (AMH) levels may be useful in reflecting the size of the primordial follicle pool. At menopause, the level is undetectable. A level above 0.5 ng/mL correlates with good ovarian reserve; levels <0.15 ng/mL suggest poor response to in vitro fertilization (IVF).[14]

Endocrine factors account for 45% to 55% of female infertility and include thyroid disease, PCOS, diabetes mellitus, prolactinemia, and luteal phase defects. Subclinical hypothyroidism, often evidenced only by high levels of TSH, decreases the chance of a successful pregnancy. This can occur even if the dysfunction is not severe enough to affect cycle regularity.[15] Clinical hypo- or hyperthyroidism can affect ovulation by interfering with normal hormonal feedback loops, and correcting thyroid disease can improve fertility.

Galactorrhea discovered during the history and physical may be caused by elevated prolactin levels, which also inhibit normal

ovulatory function. Chronically elevated prolactin levels in patients with PCOS can be attributed to elevated estrogen levels. Adiposity, acne, and hirsutism with menstrual irregularity can indicate PCOS as the primary cause, and your work-up should focus on a hyperandrogenic state.[16] Low or normal FSH levels are common in patients with PCOS. Also test for 17α-hydroxyprogestrone and serum testosterone levels.[17]

Endometriosis. How endometriosis affects fertility is controversial. One hypothesis is that it is associated with overproduction of prostaglandins, metalloproteinases, cytokines, and chemokines. The inflammatory process impairs ovarian, peritoneal, tubal, and endometrial function.[18]

Discourage the use of the postcoital test. Patients may inquire about this test, in which the cervical mucus is obtained after intercourse to assess stretch ability and sperm motility. This test has been used for more than a century, but has poor predictive value and is not recommended.[19]

Or is it him?

Inquire about sexual development and medical history, including mumps orchitis or other infections, sinopulmonary symptoms suggesting cystic fibrosis, sexually transmitted infections (STIs) and genitourinary infections, and surgical procedures of the inguinal and scrotal areas. Also ask about prescription and illicit drug use, environmental exposures, and sexual history.

Physical exam. Look for signs of androgen deficiency, such as an arm span >2 cm longer than height (eunuchoidal proportions), or loss of pubic, axillary, or facial hair.[20] Examine the external genitalia to evaluate for complete sexual development (Tanner stage of 5). The scrotum can provide clues to disorders that can affect sperm maturation and transport. Examination may reveal absence of the vas deferens, epididymal thickening, varicocele, or hernia.[21] Testicular volume, if <15 mL with testicular length <3.6 cm, can point to a decreased number of seminiferous tubules.[21]

Semen analysis. If the physical examination is normal, analyze semen for volume and pH; microscopic debris and agglutination; sperm concentration, motility, and morphology; leukocyte count; and immature germ cells. Have the man abstain from sex for 2 to 7 days before semen collection. If collection is not possible to do in the office, the patient can drop it off at a lab within an hour of collection. Analyze 2 samples at least 2 weeks apart.[22]

More detailed semen analysis can be done, especially if evaluation of the female partner does not reveal a cause of infertility. Tests include sperm autoantibodies, sperm biochemistry, semen culture, sperm function tests, and sperm-cervical mucus interaction. Typically, these tests and further evaluation of the male partner after an abnormal semen analysis are best done by a urologist specializing in reproduction.

Oligospermia or azoospermia point toward hypogonadism. Elevated morning FSH and low total testosterone correlate with primary hypogonadism, whereas low levels of both hormones correlate with secondary hypogonadism. Hyperprolactinemia is a cause of secondary hypogonadism.[3] Low volume of semen can be further evaluated by testing a postejaculatory urinalysis and transrectal ultrasonography to rule out retrograde ejaculation and ejaculatory duct obstruction.[23]

Fixing the problem

Focus initial counseling for couples on lifestyle modifications. Advise patients to quit smoking, reduce excessive caffeine and alcohol consumption, and engage in intercourse every day or every other day around ovulation. Patients should also avoid lubricants and douching as they can interfere with sperm deposition.

Managing female infertility

Tubal, pelvic, and uterine infertility. Patients with bilateral tubal obstruction may wish to undergo tubal reconstruction, especially if IVF treatments are not readily available to them. Counsel them that surgery for proximal tubal occlusion is not effective and the risk of ectopic pregnancy in the future is high, at approximately 20%.[24] Because of the low efficacy of surgery and high ectopic rate, most patients with tubal disease favor IVF. Pa-

Subclinical hypothyroidism can decrease the chances of a successful pregnancy—even if it is not severe enough to affect cycle regularity.

tients with endometriosis sometimes benefit from laser ablation or surgical resection, but often do well with intrauterine insemination (IUI) or IVF in conjunction with ovulation induction.[25] Uterine abnormalities including submucous fibroid, endometrial polyp, septate uterus, or uterine synechiae frequently benefit from surgical correction.[26] Patients with irreparable defects may want to consider a surrogate.

Ovulatory dysfunction. Anovulation can be hypogonadotropic hypogonadal (secondary to functional factors such as exercise and weight), normogonadotropic normoestrogenic with PCOS, or hypergonadotropic hypoestrogenic infertility (premature ovarian failure).

A body mass index >17 and <27 kg/m^2 is optimal to achieve fertility and to sustain a healthy pregnancy.[27] Individuals who are obese or very thin or who overexercise and do not respond to behavioral modification are known to benefit from pulsatile gonadotropin-releasing hormone therapy. This treatment, however, is not available in the United States.[28]

Dopaminergic agents can restore normal ovulation in patients with hyperprolactinemia,[29] but they should receive ovulation induction first. Patients who have glucose intolerance may benefit from an insulin-sensitizing agent such as metformin. It is particularly useful if patients also have PCOS; however, it is not an FDA-approved indication for the medication. Clomiphene has recently been shown to result in a higher rate of ovulation, but not pregnancy, than metformin.[30]

Most patients with ovulatory dysfunction are best treated with clomiphene.[31] Give 50 mg of the drug on cycle Days 3 through 7; ovulation occurs between Days 10 through 15.[12] If, after the first cycle, pregnancy has not occurred, increase the dose by 50 mg with each cycle, to a maximum of 150 mg daily.[32] Higher doses are not FDA approved, nor are they more effective. Clomiphene is most effective in the first 6 cycles, and the American Congress of Obstetricians and Gynecologists recommends limiting its use to fewer than 12 cycles due to the risk of ovarian neoplasm.[33] Clomiphene yields an ovulation rate of 73% and a pregnancy rate of 36% per cycle. Multiple births, primarily twinning, occur at a rate of 8% to 13%.[33] If clomiphene is unsuccessful, refer patients to a reproductive endocrinologist for evaluation for IVF and injectable ovulation-inducing agents.

Discourage patients from considering the postcoital test, which has poor predictive value.

Managing male infertility

Men who have hyperprolactinemic infertility can often be treated with dopaminergic agents such as bromocriptine. Inform them that normal spermatogenesis can take 3 to 6 months. Gonadotropin therapy may be effective for patients with hypothalamic or pituitary diseases. Surgery may correct obstruction, but may not actually increase pregnancy rates. Repairing a varicocele, for instance, increases sperm counts but not conception rates.[34] Other obstructive problems may need sperm extraction followed by IUI or IVF, with or without intracytoplasmic sperm injection, where the sperm is injected into the ovum in the lab before implantation.[34]

Managing unexplained infertility

Fifteen percent of infertility is unexplained.[35] Assisting these patients is challenging. Performing IUI with or without clomiphene, or giving clomiphene alone is often attempted. Pregnancy rates are 2% for expectant management, 5% for IUI alone, 9.5% for clomiphene alone, and 19% for combined IUI with clomiphene.[36] Gonadotropins are no more effective in achieving conception than clomiphene, but gonadotropin injection and IUI together are more effective than no treatment.[37] IVF, if successful, leads to pregnancy in the shortest amount of time. But it is the most costly intervention and the most likely to result in multiple births. In randomized controlled trials, however, IVF has not proved beneficial for unexplained infertility.[38]

Trends likely to affect fertility treatment

Currently in the United States, there is little regulation to guide reproductive technologies. But there is a trend, varying by state, toward legislation similar to child protection laws and adoption services, under which couples are evaluated for suitability as parents for the potential child's safety.[39] Other

countries have acts regulating reproductive technologies and infertility services. England focuses on the child's welfare; Australia restricts access by eligibility requirements.[39] In the United States we may see similar policies, especially as controversy grows regarding multiple births. Cost is a factor in the treatment of infertility. Education and household income correlate with the amount of money spent on fertility care. JFP

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In the United States, we may see reproductive technology policies similar to those in other countries—especially as controversy grows regarding multiple births.

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