Infertility

Jose-Miller AB, MD, University of Arizona, Tucson, Arizona
Boyden JW, MD, Mayo Clinic, Scottsdale, Arizona
Frey KA, MD, Mayo Clinic, Scottsdale, Arizona

Abstract

Infertility is defined as failure to achieve pregnancy during one year of frequent, unprotected intercourse. Evaluation generally begins after 12 months, but it can be initiated earlier if infertility is suspected based on history or if the female partner is older than 35 years. Major causes of infertility include male factors, ovarian dysfunction, tubal disease, endometriosis, and uterine or cervical factors. A careful history and physical examination of each partner can suggest a single or multifactorial aetiology and can direct further investigation. Ovulation can be documented with a home urinary luteinizing hormone kit. Hysterosalpingography and pelvic ultrasonography can be used to screen for uterine and fallopian tube disease. Hysteroscopy and/or laparoscopy can be used if no abnormalities are found on initial screening. Women older than 35 years also may benefit from ovarian reserve testing of follicle-stimulating hormone and estradiol levels on day 3 of the menstrual cycle, the clomiphene citrate challenge test, or pelvic ultrasonography for antral follicle count to determine treatment options and the likelihood of success. Options for the treatment of male factor infertility include gonadotropin therapy, intrauterine insemination, or in vitro fertilization. Infertility attributed to ovulatory dysfunction often can be treated with oral ovulation-inducing agents in a primary care setting. Women with poor ovarian reserve have more success with oocyte donation. In certain cases, tubal disease may be treatable by surgical repair or by in vitro fertilization. Infertility attributed to endometriosis may be amenable to surgery, induction of ovulation with intrauterine insemination, or in vitro fertilization. Unexplained infertility may be managed with ovulation induction, intrauterine insemination, or both. The overall likelihood of successful pregnancy with treatment is nearly 50 percent.

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INTRODUCTION

Infertility is defined as one year of frequent, unprotected intercourse during which pregnancy has not occurred. According to data from the National Survey of Family Growth, an estimated 10 to 15 percent of couples in the United States are infertile.[1] Many of these couples present first to their primary care physician, who may initiate evaluation and treatment. Infertility can be attributed to any abnormality in the female or male reproductive system. In most cases, the aetiology is distributed fairly equally among male factors, ovarian dysfunction, and tubal factors. A smaller percentage of cases are attributed to endometriosis, uterine or cervical factors, or other causes. In approximately one fourth of couples, the cause is uncertain and is referred to as "unexplained infertility" *(Table 1)*.[2] The aetiology is multifactorial for some couples.

EVALUATION

In general, an infertility evaluation is initiated after 12 months of unprotected intercourse during which pregnancy has not been achieved.[3,4] Earlier investigation may be considered when historical factors, such as previous pelvic inflammatory disease or amenorrhoea, suggest infertility, although physicians should be aware that earlier evaluation may lead to unnecessary testing and treatment in some cases.[3,4] Evaluation also may be initiated earlier when the female partner is older than 35 years, because fertility rates decrease and spontaneous miscarriage and chromosomal abnormality rates increase with advancing maternal age.[5,6] Partners should be evaluated together and separately, because each person may want to reveal information about which

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Men with low-volume ejaculate may benefit from postejaculatory urinalysis and transrectal ultrasonography to rule out retrograde ejaculation and ejaculatory duct obstruction.	C	4
Transvaginal ultrasonography can be used to obtain an antral follicle count and predict ovarian response to gonadotropin stimulation.	C	5, 19
Postcoital testing has not been shown to improve pregnancy outcome.	B	21
Varicocele repair has not been shown to increase the likelihood of conception.	A	26, 27
Laparoscopic ovarian drilling for ovulation induction may be beneficial in women with polycystic ovary syndrome who have not responded to other therapies.	A	29, 32
To achieve ovulation, clomiphene citrate (Clomid®) in an initial dosage of 50 mg per day is administered starting on day 3 to day 5 of the menstrual cycle and continued for five days.	C	29
Women with endometriosis may benefit from laparoscopic ablation, laparotomy, or ovulation induction with or without intrauterine insemination and in vitro fertilization.	A	35-38
Women with unexplained infertility may benefit from intrauterine insemination, clomiphene citrate therapy, or intrauterine insemination with either clomiphene citrate or gonadotropin therapy.	A	39, 40

A = consistent, good quality patient-oriented evidence; B = inconsistent or limited quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For more information about the SORT evidence rating system, see page 789 or http://www.aafp.org/afpsort.xml.

Table 1: Aetiology of infertility

Unexplained (28 percent)
Male factors (24 percent)
Ovarian dysfunction (21 percent)
Tubal factors (14 percent)
Other (13 percent)
Information from reference 2.

their partner is unaware, such as previous pregnancy or sexually transmitted disease.[7]

Evaluation of the couple

Important topics to address include the frequency and timing of intercourse, and the use of lubricants or other products that may impair fertility.[8-10] The duration of infertility and history of previous fertility for the couple and for each partner individually also need to be addressed, because they affect prognosis and may help in determining aetiology.[2,7]

Evaluation of the male partner

Any condition that results in impaired sperm quality, quantity, or both can lead to male factor infertility. Testicular failure or dysfunction, also referred to as primary hypogonadism, is the most common identifiable cause.[11] Less common causes are hypothalamic-pituitary dysfunction, also referred to as secondary hypogonadism, and conditions that affect sperm transport.[11] The aetiology remains unclear in nearly one half of cases *(Table 2)*.[4,7,11-13]

Important historical and physical examination details and laboratory tests in the evaluation of the male partner are outlined in *Table 3*.[4,7,12,13] Normal semen parameters, as established by the World Health Organization, are shown in *Table 4*.[12] If hypogonadism is

Table 2: Causes of male factor infertility

Unknown (40 to 50 percent)	Altered sperm transport (10 to 20 percent)
Primary hypogonadism (30 to 40 percent)	Absent vas deferens or obstruction
Androgen insensitivity	Epididymal absence or obstruction
Congenital or developmental testicular disorder (e.g., Klinefelter syndrome)	Erectile dysfunction
Cryptorchidism	Retrograde ejaculation
Medication (e.g., alkylating agents, antiandrogens, cimetidine [Tagamet], ketoconazole [Nizoral], spironolactone [Aldactone])	Secondary hypogonadism (1 to 2 percent)
Orchitis, including mumps orchitis	Androgen excess state (e.g., tumor, exogenous administration)
Radiation	Congenital idiopathic hypogonadotropic hypogonadism
Systemic disorder	Estrogen excess state (e.g., tumor)
Testicular trauma	Infiltrative disorder (e.g., sarcoidosis, tuberculosis)
Varicocele	Medication effect
Y chromosome defect	Multiorgan genetic disorder (e.g., Prader-Willi syndrome)
	Pituitary adenoma
	Trauma
Information from references 4, 7, and 11 through 13.	

Table 3: Key elements of infertility evaluation in men

History
Coital practices
Developmental history
Medical history (e.g., genetic disorders, chronic illness, genital trauma, orchitis)
Medications (e.g., sulfasalazine, methotrexate, colchicine, cimetidine spironolactone)
Potential sexually transmitted disease exposure, symptoms of genital inflammation (e.g., urethral discharge, dysuria)
Previous fertility
Recent high fever
Substance use
Surgical history (e.g., previous genitourinary surgery)
Toxin exposure
Physical examination
Genital infection (e.g., discharge, prostate tenderness)
Hernia
Presence of vas deferens
Signs of androgen deficiency (e.g., increased body fat, decreased muscle mass, decreased facial and body hair, small testes, Tanner stage < 5)
Testicular mass
Varicocele
Laboratory evaluation/specialized tests
Complete blood cell count (if infection suspected)
Follicle-stimulating hormone, testosterone levels (if hypogonadism suspected)
Gonorrhea and chlamydia cultures, urinalysis (if genital infection suspected)
Other laboratory studies based on history and physical examination findings
Postejaculatory urinalysis (if retrograde ejaculation suspected)
Renal and liver function studies
Scrotal ultrasonography
Semen analysis (two or more samples)
Specialized sperm studies (if initial evaluation of both partners unrevealing)
Transrectal ultrasonography (if ejaculatory duct obstruction suspected)
Information from references 4, 7, 12, and 13.

suspected based on the semen analysis (severe oligospermia or azoospermia), evaluation of morning follicle-stimulating hormone (FSH) and total serum testosterone levels can help distinguish between primary and secondary causes.[7] Elevated levels of FSH in the presence of low testosterone levels correlate with primary hypogonadism. Low levels of both hormones suggest secondary hypogonadism. Measurement of prolactin levels is indicated if secondary hypogonadism is suspected, to rule out hyperprolactinemia as the underlying cause.[7]

In patients with a low volume of ejaculate, postejaculatory urinalysis and transrectal ultrasonography may be performed to rule out retrograde ejaculation and ejaculatory duct obstruction, respectively.[4] Scrotal ultrasonography also can be helpful in evaluating suspected testicular and scrotal abnormalities such as hydroceles and tumors.[13] Specialized semen tests, including testing for sperm vitality, sperm culture, and analysis of sperm biochemistry and function, should be considered if evaluation of the female partner fails to reveal a cause.[12]

Table 4: World Health Organization 1999 seminal fluid analysis reference values

Variable	Measurement
Volume	More than 2 mL
Sperm concentration	More than 20 million per mL
Total sperm number	More than 40 million per ejaculate
Sperm motility	More than 50 percent motile and/or more than 25 percent progressively motile
Sperm morphology	More than 14 percent normal forms using strict criteria

Information from reference 12.

Table 5: Causes of female factor infertility

Ovulation disorders (40 percent)
Aging
Diminished ovarian reserve
Endocrine disorder (e.g., hypothalamic amenorrhea, hyperprolactinemia, thyroid disease, adrenal disease)
Polycystic ovary syndrome
Premature ovarian failure
Tobacco use
Tubal factors (30 percent)
Obstruction (e.g., history of pelvic inflammatory disease, tubal surgery)
Endometriosis (15 percent)
Other (about 10 percent)
Uterine/cervical factors (more than 3 percent)
Congenital uterine anomaly
Fibroids
Polyps
Poor cervical mucus quantity/quality (caused by smoking, infection)
Uterine synechiae
Information from references 2, 3, 7, 14, and 15.

Evaluation of the female partner

As previously noted, causes of infertility in the female partner include disorders of ovulation, tubal disease, and uterine or cervical factors.[2,3] Endometriosis also has been implicated as an independent cause of infertility *(Table 5)*.[2,3,7,14,15]

Important historical and physical examination details, laboratory tests, and additional studies to consider for the female partner are outlined in *Table 6*.[3,5,7,8,16-21] Details of the menstrual cycle can help determine whether the cycles are ovulatory or anovulatory. A menstrual cycle length of 22 to 35 days suggests ovulatory cycles, as does the presence of mittelschmerz and premenstrual symptoms.[14] During review of the woman's substance use history, caffeine intake should be assessed; high levels of caffeine use by the female partner have been associated with lower fertility rates.[15]

Basal body temperature charting is a simple and inexpensive means of documenting ovulation. In ovulatory cycles, the first morning body temperature often increases from 97°F to 98°F (36.1°C to 36.6°C) to greater than 98°F as a woman's menstrual cycle progresses from the follicular phase to the luteal phase. The rise in temperature is generally noted two days after a surge in luteinizing hormone (LH) occurs.[3,22] In recent years, basal body temperature charting for documentation of ovulation has largely been replaced by use of the less cumbersome urinary LH prediction kit. During ovulatory cycles, an LH surge can be detected in the urine 14 to 48 hours before ovulation.[8,16] Additionally, a single mid-luteal progesterone level, measured at the midpoint between ovulation and the start of the next menstrual cycle, can provide further confirmation as well as information about the adequacy of the luteal phase. A level greater than 6 ng per mL (19 nmol per L) implies ovulation and normal corpus luteal production of progesterone.[17] Of the three tests, the urinary LH kit provides the greatest accuracy in predicting ovulation.[17]

If ovulatory dysfunction is suspected based on the results of initial evaluation, focused laboratory investigation and other testing can help determine the underlying cause. Testing in patients with amenorrhoea, irregular menses, or galactorrhoea should involve checking FSH, prolactin, and thyroid-stimulating hormone (TSH) levels.[7,18] Low or normal FSH levels are most common in patients with polycystic ovary syndrome (PCOS) and hypothalamic amenorrhea.[18] The presence or absence of obesity and androgenisation, generally occurring in women with PCOS, can be used to distinguish between the two disorders.[18] The usefulness of the progesterone challenge test is limited because of high false-positive and false-negative rates with respect to the presence or absence of oestrogen production.[18] A high FSH level correlates with ovarian failure.[18] Evaluation of prolactin level is useful to rule out pituitary tumor, and measurement of TSH is necessary to rule out hypothyroidism.[18] Measurement of 17alpha-hydroxyprogesterone and serum testosterone levels is helpful in evaluating patients with hyperandrogenism for late-onset congenital adrenal hyperplasia and androgen-secreting tumors.[23]

Women older than 35 years may benefit from testing of FSH and oestradiol levels on day 3 of their menstrual cycle to assess ovarian reserve.[5] An FSH level of less than 10 mIU per mL (10 IU per L), combined with an oestradiol level of less than 80 pg per mL (294 pmol per L), suggests favourable follicular potential.[5] The clomiphene citrate challenge test, in which the FSH level is obtained on day 3 of the cycle, then again on day 10 after administration of clomiphene citrate (Clomid®; 100 mg per day) on days 5 to 9, also can be helpful in assessing ovarian reserve.[5] Normal and abnormal values vary by laboratory. Obtaining an antral follicle count via transvaginal ultrasonography can be useful in evaluating ovarian reserve; it also can help predict ovarian responsiveness to gonadotropin stimulation, which is useful when considering treatment options.[5,19] The optimal test to assess ovarian reserve has not yet been determined.[5] Circulating inhibin B levels and the gonadotropin-releasing hormone test are not recommended for routine use in the assessment of ovarian reserve because of limited data regarding their prognostic value.[5]

If the initial history and physical examination suggest tubal dysfunction or a uterine abnormality, or if other testing has failed to reveal an aetiology, hysterosalpingography is indicated.[3,7] The contour of the uterine cavity, including the presence or absence of any abnormalities, as well as tubal patency can be assessed. Ultrasonography can also be

used to evaluate for pelvic pathology.[3] If abnormalities are detected, hysteroscopy and/or laparoscopy, depending on the location of the abnormality, can be pursued for confirmation and further assessment.[3,7] Laparoscopy may be performed as a final step in the infertility evaluation because it can reveal additional causes not otherwise seen, including endometriosis and pelvic adhesions.[3,7,20] The use of postcoital testing to evaluate for factors of cervical mucus has been abandoned by most physicians because of its lack of effect on pregnancy outcome.[21]

MANAGEMENT

Treatment of the couple

Ideal coital frequency, consisting of intercourse on multiple days during the "fertile window," which includes the five days preceding and the day of anticipated ovulation, should be reviewed with the couple.[8] Using the Clear Plan Easy Fertility Monitor, checking for E-type vaginal mucous discharge (i.e., clear, stringy), or both, may be the most helpful in determining optimal timing of intercourse, because they reflect the increase in oestrogen before the LH surge and are more prospective than basal body temperature charting or the urinary LH kit.[8]

The importance of avoiding lubricants and douches should be stressed.[10] Both partners should be encouraged to avoid alcohol consumption and use of tobacco and street drugs and, as mentioned earlier, the woman should be counselled to limit caffeine intake.[3,4,7,15] The use of fertility-impairing medications should be avoided by both partners if possible *(Tables 3 and 6).*[2,3,7,12,14,15]

The couple should be offered emotional support because infertility often produces significant stress and sadness in one or both partners. Groups such as RESOLVE: the National Fertility Association can provide additional support and information to assist the couple (http://www.resolve.org).

Management of male factor infertility

Dopamine agonists such as bromocriptine (Parlodel®) can be useful in patients with hyperprolactinemia.[24] Agents to treat erectile dysfunction can be employed if indicated.[25] If obstruction or a varicocele is found to be associated with seminal fluid abnormalities, surgical repair may be pursued. Varicocele repair has been shown to improve semen parameters, although it has not yet been shown to increase the chance of conception.[26,27] In general, seminal fluid abnormalities warrant referral to a fertility specialist for treatment. Depending on findings, treatment options available to the specialist include gonadotropin injections, intrauterine insemination, and in vitro fertilization (IVF) with or without intracytoplasmic sperm injection, using testicular sperm extraction if indicated.[25,28]

Management of ovulatory dysfunction

Underlying causes of ovulatory dysfunction, such as thyroid dysfunction, should be corrected if possible.[29] As with men, women who have hyperprolactinemia can be treated with dopaminergic agents, which may restore ovulation.[30] Insulin-sensitizing agents, most commonly metformin (Glucophage®), have been shown to increase ovulation and pregnancy rates in patients with PCOS, although these agents are not yet approved by the U.S. Food and Drug Administration (FDA) for the treatment of infertility.[31] Laparoscopic ovarian drilling for ovulation induction also may be considered for patients with PCOS if other treatments are unsuccessful.[29,32]

In most women with ovulatory dysfunction without evident cause or that is not otherwise correctable, the condition can be managed with use of the oral ovulation-inducing agent clomiphene citrate.[29] Clomiphene citrate can be used in patients with PCOS as well, with or without the coadministration of insulin-sensitizing agents.[31] Treatment with clomiphene citrate is ineffective in patients with ovulatory dysfunction caused by hypothalamic amenorrhea, however, because its mechanism of action occurs at the hypothalamus.[29] These patients are more likely to respond to gonadotropin therapy.[14] Women with limited ovarian reserve also are unlikely to benefit from ovulation induction. Currently, only oocyte donation has been proven successful for these patients.[5]

Clomiphene citrate is generally well tolerated and effective; 80 percent of appropriately selected patients will ovulate with this treatment.[29] Major risks associated with the use of clomiphene citrate include ovarian hyperstimulation syndrome and twinning. Higher-order multiple gestation is a rare consequence.[29] Generally, a dosage of 50 mg per day is administered starting on day 3 to day 5 of the menstrual cycle and is continued for five days.[29] Documentation of ovulation can be accomplished

Table 6: Key elements of infertility evaluation in women

History
Coital practices
Medical history (e.g., genetic disorders, endocrine disorders, history of pelvic inflammatory disease)
Medications (e.g., hormone therapy)
Menstrual history
Potential sexually transmitted disease exposure, symptoms of genital inflammation (e.g., vaginal discharge, dysuria, abdominal pain, fever)
Previous fertility
Substance use, including caffeine
Surgical history (previous genitourinary surgery)
Toxin exposure
Physical examination
Breast formation
Galactorrhoea
Genitalia (e.g., patency, development, masses, tenderness, discharge)
Signs of hyperandrogenism (e.g., hirsutism, acne, clitoromegaly)
Laboratory evaluation/specialized tests
To document ovulation: measurement of mid-luteal progesterone level, urinary luteinizing hormone using home prediction kit, and basal body temperature charting
To determine etiology if ovulatory dysfunction suspected: measurement of FSH, prolactin, thyroid-stimulating hormone, 17alpha-hydroxyprogesterone (if hyperandrogenism suspected), testosterone (if hyperandrogenism suspected)
To assess ovarian reserve (women older than 35 years): measurement of FSH and oestradiol levels on day 3 of the menstrual cycle, clomiphene citrate (Clomid®) challenge test, or transvaginal ultrasonography for antral follicle count

fairly easily with basal body temperature charting or use of a urinary LH kit.[29] If a dosage of 50 mg per day is insufficient to induce ovulation, it can be increased to 100 mg per day. Higher dosages generally should be managed by a fertility specialist because 100 mg per day is the maximal dosage approved by the FDA.[29] If clomiphene citrate therapy is unsuccessful, additional treatment options include IVF and injectable ovulation-inducing agents such as human menopausal gonadotropin, exogenous FSH, and gonadotropin-releasing hormone.[33]

Management of tubal, uterine, and pelvic disease

Tubal disease may be treated with tubal reparative surgery, although success rates are generally low and are compromised by increased risk of subsequent ectopic pregnancy.[14,34] IVF is an alternative, especially in patients with markedly damaged tubes.[14] Patients with endometriosis may benefit from laparoscopic ablation or laparotomy, depending on the severity of disease.[35,36] Ovulation induction with or without intrauterine insemination and IVF also can be used in these patients.[35,37,38]

Management of unexplained or persistent infertility

Options for patients with unexplained infertility include intrauterine insemination, clomiphene citrate therapy, and intrauterine insemination with either clomiphene citrate or gonadotropin therapy.[39,40] To date, the benefit of IVF has not been proven in patients with unexplained infertility.[41] IVF may be useful in patients with persistent infertility in whom treatments for specific diagnoses have been unsuccessful.[14]

PROGNOSIS

The overall likelihood of successful treatment for infertility is nearly 50 percent, but this varies by cause, age of the female partner, history of previous fertility, and duration of infertility.[42] Of the various aetiologies, infertility attributed to ovulatory dysfunction has the best prognosis, with treatment success rates approaching 50 percent overall. Infertility caused by tubal factors or severe endometriosis has the least likelihood for success (i.e., 21 and 17 percent, respectively).[42] A shorter duration of infertility and previous fertility increase the chance of achieving pregnancy, as does age younger than 30 years in the female partner.[2,7,42]

The Authors

ALAINA B. JOSE-MILLER, M.D., is an assistant clinical professor in the Department of Family and Community Medicine at the University of Arizona, Tucson. Dr. Jose-Miller received her medical degree from Loyola University Chicago Stritch School of Medicine, Maywood, Ill., and completed a family medicine residency at the Good Samaritan Family Practice Program, Phoenix, Ariz.

JENNIFER W. BOYDEN, M.D., is a consultant in the Department of Family Medicine at the Mayo Clinic, Scottsdale, Ariz., and an assistant professor of family medicine at the Mayo Clinic School of Medicine, Scottsdale. She received her medical degree from the University of Utah Medical School, Salt Lake City, and completed residency training at Mayo Clinic, Scottsdale, Family Practice Residency.

KEITH A. FREY, M.D., M.B.A., is chair of the Department of Family Medicine, Mayo Clinic, Scottsdale, and an associate professor of family medicine at Mayo Clinic School of Medicine. He received his medical degree from the Medical College of Virginia, Virginia Commonwealth University, Richmond, and completed a residency in family practice at the U.S. Air Force Medical Center, Scott Air Force Base, Ill.

Address correspondence to Alaina B. Jose-Miller, M.D., Dept. of Family and Community Medicine, University of Arizona, 707 N. Alvernon Way, Suite 101, Tucson, AZ 85711. Reprints are not available from the authors.

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