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Evaluation and Management of Infertility

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ABSTRACT

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse. Approximately 85% of infertile couples have an identifiable cause. The most common causes of infertility are ovulatory dysfunction, male factor infertility, and tubal disease. The remaining 15% of infertile couples have "unexplained infertility." Lifestyle and environmental factors, such as smoking and obesity, can adversely affect fertility.

Ovulatory disorders account for approximately 25% of infertility diagnoses; 70% of women with anovulation have polycystic ovary syndrome. Infertility can also be a marker of an underlying chronic disease associated with infertility. Clomiphene citrate, aromatase inhibitors such as letrozole, and gonadotropins are used to induce ovulation or for ovarian stimulation during in vitro fertilization (IVF) cycles.

Adverse effects of gonadotropins include multiple pregnancy (up to 36% of cycles, depending on specific therapy) and ovarian hyperstimulation syndrome (1%–5% of cycles), consisting of ascites, electrolyte imbalance, and hypercoagulability. For individuals presenting with anovulation, ovulation induction with timed intercourse is often the appropriate initial treatment choice.

For couples with unexplained infertility, endometriosis, or mild male factor infertility, an initial 3 to 4 cycles of ovarian stimulation may be pursued; IVF should be considered if these approaches do not result in pregnancy. Because female fecundity declines with age, this factor should guide decision-making. Immediate IVF may be considered as a first-line treatment strategy in women older than 38 to 40 years. IVF is also indicated in cases of severe male factor infertility or untreated bilateral tubal factor.

Keywords-evalution, prevention, diagnosis and treatment

INTRODUCTION

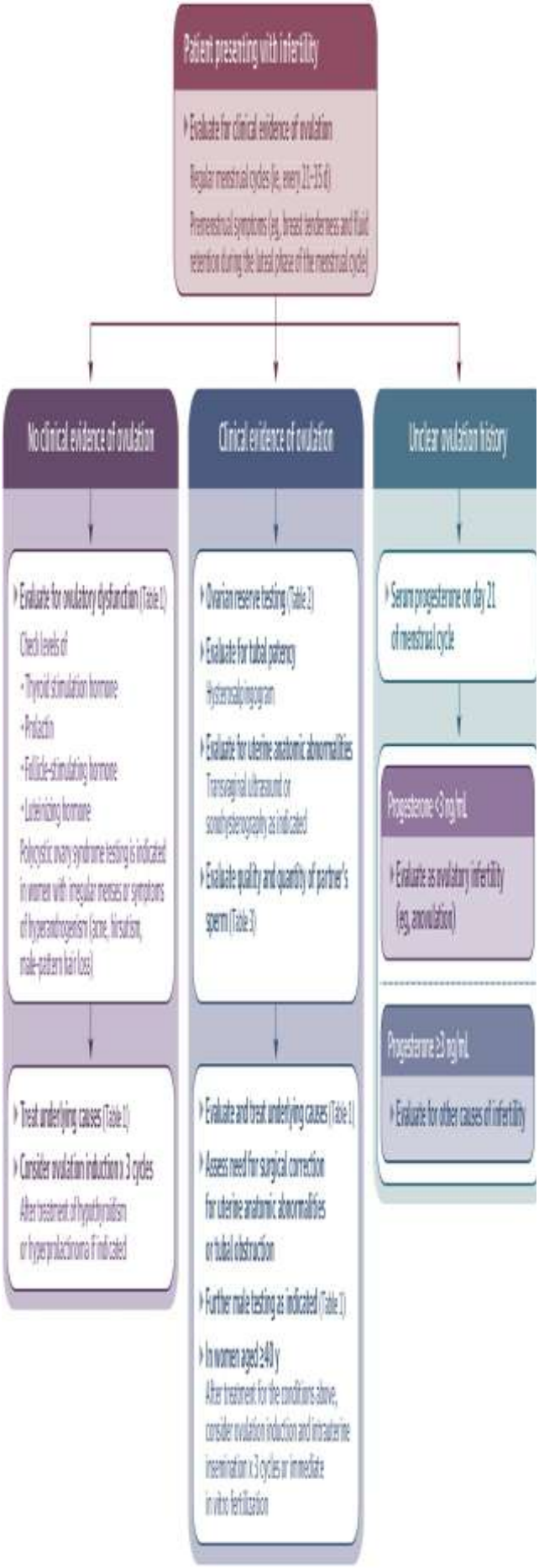
Infertility, defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse, affects 8.8% of US women aged 15 to 49 years[1] and is often associated with significant physical and emotional stress. This review summarizes current evidence regarding the pathophysiology, diagnosis, and management of infertility for heterosexual couples.[2]

Approach to the Patient with Infertility
Heterosexual women desiring pregnancy who have not conceived after 12 months of unprotected intercourse or donor insemination should be offered an infertility evaluation.

Earlier evaluation is recommended for women older than 35 years who have not conceived for 6 months, and more immediate evaluation is warranted for women older than 40 years.[3] Fertility evaluation is also recommended for women with oligomenorrhea or amenorrhea, known or suspected uterine, tubal, or peritoneal disease (including stage III or IV endometriosis), and male partners with known or suspected male factor infertility (Figure).[4]

Infertility is caused by identifiable abnormalities in normal physiology or underlying disease in 85% of infertile couples.

The most common causes of infertility are ovulatory dysfunction, male factor infertility, and tubal disease. The remaining 15% of infertile couples have "unexplained infertility."[5]
Figure.



Suggested Evaluation for Patients Presenting With Infertility Women who have not achieved pregnancy after 12 months of unprotected intercourse or donor insemination should be offered an infertility evaluation. Earlier evaluation is recommended for women older than 35 years who have failed to conceive for 6 months; for women older than 40 years, immediate evaluation is warranted.[3] Evaluation is also recommended for women with oligomenorrhea or amenorrhea, known or suspected uterine, tubal disease, or peritoneal disease (including stage III or IV endometriosis) and known or suspected male infertility.[4]

Major Categories of Infertility

Ovulatory Dysfunction and Anovulation

A history of regular, cyclic menstrual cycles with premenstrual symptoms (eg, breast tenderness, fluid retention) is adequate to establish ovulation. According to the World Health Organization, ovulatory disorders (Table 1)[6–10] account for approximately 25% of infertility diagnoses.[11] Anovulation should be suspected when menstrual cycles occur irregularly, in cycles shorter than 21 or longer than 35 days (although for most women, cycle length is >25 days), or if the patient reports abnormal uterine bleeding or amenorrhea.[9]

Ovulation typically occurs 14 days before onset of menstruation. When the menstrual history is unclear or inadequate, ovulation may be documented with a postovulatory serum progesterone level obtained in the expected midluteal phase, approximately 1 week before the expected menses. The most common cause of anovulation is polycystic ovary syndrome (PCOS),[12] which affects 70% of women with anovulation.

Obesity itself is associated with anovulation apart from PCOS; women with a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) greater than 27 have an increased risk of anovulatory infertility compared with women with a normal-range BMI (relative risk, 3.1 [95% CI, 2.2–4.4]; absolute rates were not given in the American Society for Reproductive Medicine guideline).[13]

Other causes include thyroid disease (2%–3%), pituitary disease (eg, prolactinoma, 13%), elevated androgens from adrenal hyperplasia or adrenal tumor (2%), idiopathic chronic anovulation (7%–8%), and functional hypothalamic amenorrhea (eg, due to underweight, eating disorders, and excessive exercise). Patients with eating disorders have anovulatory infertility more often than women without an eating disorder (16.2% vs 5.6%; n = 271).[14]

Table 1.

Category	Categories and examples of infertility etiology	Diagnostic testing	Treatment
Ovulatory dysfunction[b]	Thyroid dysfunction; hyperprolactinemia; PCOS, hypothalamic amenorrhea	History and physical examination; TSH, prolactin If PCOS is suspected: free and total testosterone; DHEAS; 17-OHP; transvaginal ultrasound FSH/LH/estradiol	Abnormal TSH or prolactin: correction of the specific defect can stimulate ovulation PCOS: ovulation induction (unless other infertility factors are present); for obese women, weight loss of 15% of body weight can prompt ovulation to resume[6] Hypogonadotropic hypogonadism may be treated with pulsatile GnRH or gonadotropin therapy; hypergonadotropic hypogonadism may necessitate donor oocytes
Tubal occlusion[c]	Related to sexually transmitted infections; endometriosis; peritubal adhesions; hydrosalpinx	Hysterosalpingogram (sensitivity: 65%; specificity: 83%) Laparoscopy with chromotubation (ie, instillation of a fluid through the tubes and visualization of it spilling from the tube)	Surgical repair (eg, hysteroscopy with tubal cannulation for proximal tubal obstruction, tubal reanastomosis, or fimbrioplasty for distal obstruction) or IVF
Endometriosis[d]	Risk factors include early menarche, short menstrual cycles, heavy menstrual periods, nulliparity, and family history of endometriosis	Transvaginal ultrasound	Diagnostic laparoscopy has minimal therapeutic benefit in women with mild endometriosis and typically is not warranted to rule out endometriosis in asymptomatic women with infertility Ovulation induction (see Table 4) vs IVF if other infertility factors are present
Diminished ovarian reserve[e]	Age-related oocyte loss Chemotherapy/radiation Fragile X premutation[f]	Ovarian reserve testing (eg, AMH, FSH/estradiol, AFC; see Table 2)	Variable, depending on age/history and ovarian reserve testing
Uterine factors[g]	Endometrial polyps/fibroids, uterine synechiae	TVUS Sonohysterogram 3-D ultrasound/MRI	Hysteroscopic removal, as appropriate
Male factors[h]	Obstructive causes (eg, cystic fibrosis mutation, retrograde ejaculation); nonobstructive causes (eg, testicular failure)	Semen analysis (repeat if abnormal) If sperm count <10 million/mL or symptoms/examination findings suggest endocrinopathy,[7] FSH and total testosterone, prolactin, karyotype/Y chromosome microdeletion testing[i] Physical examination: ultrasound if findings suggest varicocele; cystic fibrosis testing if findings suggest absent vas deferens Routine use of other sperm testing (such as antisperm antibodies, sperm DNA fragmentation, or sperm chromosome aneuploidy) is controversial and generally not recommended[7]	Treatment based on results of initial evaluation Diagnostic testing and consultation with a reproductive specialist if indicated based on results of the initial evaluation; see Penzias et al[8] for comprehensive evaluation and management[j] Surgical repair, surgical sperm retrieval, and/or IUI or IVF with ICSI, as indicated

Categories of Infertility, Potential Testing, and Treatment Options[a]
Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; 17-OHP, 17-hydroxyprogesterone; PCOS, polycystic ovary syndrome; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone; TVUS, transvaginal ultrasound.

a

Infertility is attributable to an identifiable cause as outlined in the table in 85% of women and couples; however, 15% of couples have unexplained infertility[5] after diagnostic workup has been completed.

b

Testing indicated if menstrual cycles are irregular or patient reports abnormal uterine bleeding or amenorrhea; also indicated if serum progesterone levels are suggestive of anovulation (see the Ovulatory Dysfunction and Anovulation section).

c

Testing may be deferred in anovulatory infertile women but should be performed if the patient does not conceive after 3 to 6 cycles of successful ovulation induction.[9]

d

Testing indicated if patient reports cyclic or chronic pelvic pain, dysmenorrhea, or dyspareunia or if examination demonstrates adnexal mass and/or uterosacral ligament nodularity, thickening, or tenderness.[10]

e

Testing indicated for women at increased risk of diminished ovarian reserve (age >35 years, family history of early menopause, prior ovarian surgery or absent ovary, history of chemotherapy or pelvic radiation).

f

A premutation is defined as 55 to 200 unmethylated CGG repeats in the 5′ UTR of the X-linked *FMR1* gene.

g

Testing may be deferred in anovulatory infertile women but should be performed if patient does not conceive after 3 to 6 cycles of successful ovulation induction.[9]

h

Testing indicated for all male partners of couples presenting for infertility evaluation or in men presenting with risk factors for male factor infertility (eg, history of chemotherapy or pelvic radiation, prior testicular surgery).[7]

i

In cases of nonobstructive azoospermia, a 2019 systematic review and meta-analysis of 117 studies found surgical sperm retrieval rates of 47%, with live birth rates of 24% per ART cycle using retrieved sperm.

j

Testing for a mutation in the azoospermic factor (AZF) region, found on the long arm of the Y chromosome, can help guide decision-making regarding sperm retrieval. Complete deletions in the AZFa region result in azoospermia; men with deletions in the AZFb and AZFb-c regions frequently also have azoospermia (19 of 21 patients or 90.5% in a prospective study of infertile men). A Y chromosome defect in a man is transmissible to his male offspring, and genetic counseling should be considered before undertaking ART.

Tubal Infertility

Tubal infertility, defined as either blocked fallopian tubes or inability of the tubes to pick up an oocyte from the ovary due to pelvic adhesions, accounts for between 11%[11] and 67%[15] of infertility diagnoses, depending on the population studied. Tubal infertility should be suspected in women with a history of sexually transmitted infection (the most common cause of tubal disease[16]), cervical dysplasia, abdominal surgery, or previous intraabdominal infection (eg, ruptured appendix). The severity of tubal abnormalities helps determine the most effective treatment. Hysterosalpingography (HSG), a procedure in which radiopaque dye (either oil or water soluble) is injected through the uterine cervix into the uterine cavity and followed through the fallopian tubes with fluoroscopy, has a sensitivity and specificity of 65% and 83%, respectively,[17] and is a first-line diagnostic tool for tubal infertility. A recent systematic review and meta-analyses of 6 RCTs determined that the use of oil-soluble contrast media (OSCM) was associated with significantly higher rates of pregnancy (defined as a positive fetal heartbeat on ultrasonographic examination after 12 weeks' gestation) after HSG compared with water-soluble contrast media (WSCM) (rates were 32.1% for oil contrast vs 23.6% for water contrast).[18] In one study of 1119 women randomly assigned to HSG with OSCM or WSCM, 379 ongoing pregnancies were observed in the OSCM group vs 326 ongoing pregnancies in the WSCM group (odds ratio, 1.47 [95% CI, 1.12–1.93]).[19] The underlying mechanisms by which oil contrast might enhance fertility are unclear. Sonohysterography (SHG), in which spillage of contrast from the fallopian tubes is introduced into the uterine cavity and assessed with ultrasound, can be used to assess tubal patency with a sensitivity and specificity of 76% and 67%, respectively.[20] Laparoscopy with chromopertubation, in which indigo carmine is inserted transcervically into the uterus and evaluated directly for tubal spillage with

laparoscopic visualization, is considered the gold standard for evaluating tubal disease.

Compared with infertile women with bilateral tubal patency, those with unilateral proximal tubal blockage have similar pregnancy rates after ovarian stimulation with intrauterine insemination.[21] However, when bilateral tubal obstruction exists, surgery to restore tubal patency or ovarian stimulation with in vitro fertilization (IVF) can be considered. To our knowledge, there are no high-quality RCTs comparing surgery vs IVF for tubal infertility. The selection of tubal surgery or IVF (which bypasses tubal blockage) should be based on the female partner's age, infertility duration, and presence of other diagnoses (such as male factor infertility), prior pregnancy success and number of desired pregnancies, extent of tubal disease, and financial resources. For example, a woman who is younger than 35 years, has no other infertility factors, and desires more than 1 child may opt for tubal surgery, especially if she does not have the financial resources to support IVF. Laparoscopic tubal ligation (interruption of the tubes) or salpingectomy (removal of the fallopian tubes) should be considered prior to IVF in women with hydrosalpinges (fluid-filled fallopian tubes, typically due to a long-standing untreated infection involving the fallopian tubes). This approach increases the clinical pregnancy rate (396 clinical pregnancies in the surgical treatment group per 1000 patients vs 123 clinical pregnancies per 1000 patients in the nonsurgical group; risk ratio, 3.21 [95% CI, 1.72–5.99]; 2 RCTs).[22]

Endometriosis

Endometriosis is the presence of endometrial tissue outside the uterine cavity and affects 25% to 40% of women with infertility.[23] Anatomic distortion, such as the presence of adhesions blocking the fallopian tubes or impairing tubal patency, or ovarian masses (eg, endometriomas) occurring between the tube and site of ovulation can impair tubal patency, oocyte quality, and retrieval of oocytes by tubal fimbria.[24] Data are conflicting regarding whether endometriosis can affect endometrial receptivity.[25] Although laparoscopic surgery for endometriosis improves spontaneous pregnancy rates,[26] it is not recommended as part of a routine fertility evaluation in women without endometriosis symptoms.[24]

Diminished Ovarian Reserve

In a study of fecundity in women undergoing artificial insemination with frozen donor semen, cumulative success rates over 12 cycles were 74.1% for the group aged 26 to 30 years, 61.5% for the group aged 31 to 35 years, and 53.6% for the group older than 35 years.[27] This decline in fecundity with older age occurs in part due to the progressive loss of follicles and oocytes (the "ovarian reserve") and the deterioration of gamete quality with age. Other risk factors for diminished ovarian reserve include a history of ovarian surgery, chemotherapy, radiation therapy with exposure to the ovaries, a family history of premature menopause, or a fragile X (*FMR1*) pre-mutation, defined as between 55 and 200 CGG repeats in the fragile X gene. Ovarian reserve can be assessed with serum markers such as anti-Müllerian hormone or ultrasound (Table 2).[8,28–36] Anti-Müllerian hormone, which is expressed by small growing ovarian follicles and declines with age, reflects the size of the follicular pool and correlates with the number of oocytes retrieved after ovarian hyperstimulation.[37] As the follicle pool diminishes in size, inhibition of pituitary follicle-stimulating hormone (FSH) secretion by estrogen is lost and early follicular phase serum FSH rises. As ovarian reserve diminishes further, early follicular phase estradiol rises and inhibits FSH elevation.

Table 2.
Tests to Assess Ovarian Reserve[a]

Test	Description	Timing	Thresholds suggesting increased probability of low ovarian reserve	Cost[b]
AMH[28–30]	Glycoprotein produced by granulosa cells of growing follicles High predictive value for ovarian response to stimulation May be decreased in patients with obesity[31,32] Interpretation of AMH is laboratory assay-dependent	Low intercycle variability; can be performed throughout cycle	<1.66 ng/mL[33]	$76-$95[34]
FSH and estradiol	FSH is secreted by pituitary; early follicular levels reflect unsuppressed hypothalamic-pituitary-ovarian axis function Significant intra- and intracycle variability; thus, a highly abnormal FSH (eg, >15 mIU/mL) is specific for DOR but less sensitive than AMH and does not detect more subtle declines in ovarian reserve[35] Estradiol is useful in interpreting FSH concentrations;	Early follicular phase (if patient has regular menstrual cycles) or random (if suspected anovulation)	FSH >10–15 mIU/mL Estradiol >60–80 pg/mL	$95-$125[34]

	prospective studies suggest that day 3 estradiol levels >80pg/mL result in higher cycle cancellation rates and lower pregnancy rates			
Antral follicle count[34]	Sum of follicles measuring 2–10 mm in both ovaries observed by ultrasound Good intercycle reliability Limited ability to evaluate overweight or obese women Should be performed in experienced centres	Can be performed throughout cycle	<4 Follicles 2–10 mm in both ovaries	$300-$500[3,4]

Abbreviations: AMH, anti-Müllerian hormone; DOR, diminished ovarian reserve; FSH, follicle-stimulating hormone.
[a]

In general, there is not consensus on the threshold values suggestive of reduced fertility potential; listed thresholds are suggestive of low ovarian reserve and/or ovarian response to stimulation.

Uterine and Cervical Factors

Uterine cavity abnormalities are associated with adverse pregnancy outcomes such as miscarriage and preterm birth (outcomes that are not limited to infertile women).[28,38] Factors that distort the uterine cavity include endometrial polyps, leiomyomas, intrauterine synechiae, and congenital uterine malformations such as septate uterus.

SHG detects polyps or leiomyomas with a sensitivity and specificity of 91% and 84%, respectively, making SHG superior to HSG and transvaginal ultrasound for evaluating the uterine cavity. If a congenital malformation (eg, bicornuate uterus) is suspected, further evaluation with pelvic magnetic resonance imaging or 3-dimensional ultrasound is warranted. To our knowledge, there is no high-quality evidence to support the routine use of hysteroscopy as a diagnostic test for infertility aetiology in the general population of infertile women with a normal ultrasound or HSG.

Surgery to correct uterine cavity defects is commonly performed to improve reproductive outcomes. A 2018 Cochrane review based on 2 RCTs including 309 women compared operative hysteroscopy vs control for suspected uterine cavity abnormalities including uterine fibroids, endometrial polyps, intrauterine adhesions, and uterine septum.

It concluded that removing endometrial polyps may improve pregnancy rates, but that more research is needed to measure the effectiveness of surgery on other structural uterine abnormalities. A 2015 Cochrane review of 2 randomized trials found very low–quality evidence to support hysteroscopic removal of submucous fibroids for infertile women (39% clinical pregnancy rate after surgery vs 21% without surgery among 94 women; odds ratio, 2.44 [95% CI, 0.97–6.17]; $P = .06$). Although limited, based on these data, surgery is frequently considered for infertile women with cavity-distorting defects, especially if other symptoms (eg, abnormal uterine bleeding) are present.

Male Factor

Disorders of male physiology, such as low testosterone concentrations or low sperm count, occur in 35% of infertile couples.[41] A couple may also have multiple factors contributing to infertility; therefore, an evaluation for male factor infertility should be performed concurrently to the female evaluation. In addition to a reproductive history, semen analysis should be performed to determine semen volume and sperm production (Table 3) When the ejaculate does not contain sperm (azoospermia), the presence of sperm in a urine specimen confirms retrograde ejaculation.

Obstructive azoospermia is defined as the absence of sperm in the ejaculate due to an obstruction of sperm transport. In men with obstructive azoospermia, the finding of congenital bilateral absence of the vas deferens should prompt evaluation for a mutation in the cystic fibrosis transmembrane conductance regulator, the protein absent in patients with cystic fibrosis.

The most common cause of nonobstructive azoospermia is primary testicular failure, a diagnosis that requires serum total testosterone and FSH levels and subsequent testing based on initial results (Table 1). Treatment for azoospermia includes surgical sperm retrieval from the testes to obtain sperm for immediate use in assisted reproductive technology (ART) cycles or cryopreservation for later use.

Table 3.
World Health Organization Lower Limits of Normal Semen Parameters

Parameter	**Normal values**
pH	7.2–7.8
Volume	1.5 cc
Total count	39 million
Concentration	≥15 Milllion sperm/mL(<15 million sperm/mL indicates oligozoospermia)
Motility	≥40% Forward progression (<40% forward progression indicates asthenozoospermia)
Morphology	≥4% Normalforms (by Kruger criteria[42]) (<4% normally formed sperm indicates teratospermia) 4
White blood cell count	<1 Million/μL

Total motile sperm count (TMC), or the number of moving sperm in the entire ejaculate, can be calculated by multiplying the volume by the concentration (million sperm/mL) by the motility (% moving). TMCs less than 20 million are significantly associated with a lower probability of fathering a child. Values are based on samples from men who had fathered a pregnancy in the previous year and taken after 2 to 7 days of abstinence. Values represent the fifth percentile. A diagnosis of an "abnormal" semen analysis should only be made after a repeat analysis is performed, at least 1 month later.

Treatment for Infertility

Commonly used infertility treatments include ovulation induction, which refers to the use of pharmacologic treatments to induce ovulation, and ovarian stimulation, which is performed with the goal of inducing multiple mature ovarian follicles. Either timed intercourse or intrauterine insemination (IUI) may be used to achieve fertilization at the time of ovulation. Alternatively, mature oocytes may be retrieved directly from the ovary for fertilization using an ultrasound-guided needle (IVF).

Treatment Options

Two oral medications are used for ovulation induction. Clomiphene citrate is a selective estrogen receptor modifier that blocks the negative feedback effect of circulating estradiol and causes an increased hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and subsequent pituitary FSH and luteinizing hormone (LH) production,[45] promoting ovarian follicular growth. Letrozole blocks aromatase, reducing serum concentrations of estradiol and stimulating pituitary gonadotropins. Both clomiphene citrate and aromatase inhibitors have a multiple pregnancy rate of less than 10%, the majority of which are twin gestations. n women with PCOS undergoing ovulation induction, letrozole is the first-line therapy based on the Pregnancy in Polycystic Ovary II Trial, which demonstrated that letrozole results in higher live birth rates compared with clomiphene (103 of 374 [27.5% live birth rate] vs 72 of 376 [19.1% live birth rate]). A 2018 Cochrane review of 13 RCTs involving 2954 women comparing clomiphene vs letrozole reached a similar conclusion (314 pregnancies per 1000 women treated with letrozole vs 214 pregnancies with clomiphene; odds ratio, 1.68 [95% CI, 1.42–1.99]), without differences in ovarian hyperstimulation rates, miscarriage rates, or multiple pregnancy rates.

Table 4.
Medications to Treat Infertility[a]

Example	**Dose**	**Adverse effects (rate)**	**Efficacy**
Selective estrogen receptor modifiers, used for ovulation induction			
Clomiphene citrate	50 mg/daily orally × 5 d (starting between cycle days 2 and 5 after an induced or spontaneous bleed); may increase up to 150 mg/daily if ovulation does not occur[b]; identification of an ovulatory LH surge for timing of intercourse or IUI can be done using urinary LH kits or office estradiol/ultrasound	Hot flashes (33%), headache (34%), fatigue (14%), dizziness (7%), irritability (21%); thin endometrium (15%−50%[49]); visual disturbances (2%); multiple pregnancy (up to 12.5%)[45]	24%−31% Cumulative LBR over 3 cycles when combined with IUI for unexplained infertility[8]; 19.1% LBR over 5 cycles in women with PCOS[46]
Aromatase inhibitors, used for ovulation induction (off-label indication)			
Letrozole	2.5 mg/daily orally × 5d (starting between cycle days 2 and 5 after an induced or spontaneous bleed); may increase up to 7.5 mg/daily if ovulation does not occur; monitoring for ovulation as with clomiphene citrate	Hot flashes (20.3%), headache (41%), fatigue (21.7%), dizziness (12.3%), irritability (18%); multiple pregnancy (up to 14.3%)[50] In contrast to clomiphene, letrozole does not	27.5% Cumulative LBR over 5 cycles in women with PCOS[46]

		appear to adversely affect endometrial thickness and cervical mucus[50]	
Gonadotropins, used for ovarian stimulation in combination with timed intercourse/IUI or IVF			
Follicle-stimulating hormone: urinary FSH (Bravelle) recombinant follitropin beta (Follistim); recombinant follitropin alpha (Gonal-F)	For ovarian hyperstimulation with timed intercourse or IUI: typical starting dose is 37.5–75 IU/d; for IVF, typical starting dose is 150–200 IU/d	Injection site reaction (10%), abdominal bloating/discomfort (27%−34%); ovarian hyperstimulation syndrome (1%−5% of cycles)[51]; multiple pregnancy (up to 36%)[52]	32%−33% Cumulative LBR over 4 cycles when used in combination with IUI for ovarian stimulation; depending on age, LBR may be >65% per cycle when used for IVF with autologous oocytes[8]
LH: recombinant luteotropin alpha (Luveris)			
Human menopausal gonadotropin: Menopur, Repronex			
Human chorionic gonadotropin (hCG), used as an ovulatory trigger in ovulation induction and ovarian hyperstimulation cycles			
Recombinant hCG (Ovidrel)	250-μg Recombinant hCG	Injection site swelling, pain, erythema (10%−20%)	Based on OI or OS regimen used
Urinary hCG (Pregnyl, Novarel)	5000–10 000 Units of urinary hCG		
GnRH agonists, used for pituitary downregulation and as an ovulatory trigger during ovarian hyperstimulation cycles			
Leuprolide acetate (Lupron)	Injection: 0.5–1 mg subcutaneous daily	Short-term menopausal symptoms (eg, hot flashes, mood swings, vaginal dryness, headache) (70%−80%)	Based on OI or OS regimen used
Nafarelin acetate (Synarel)	Nasalspray: 400 μg twice daily		
GnRH antagonists, used for pituitary downregulation during ovarian hyperstimulation cycles			
Ganirelix; Cetrorelix acetate (Cetrotide)	Injection: 0.25 mg daily	Similar to GnRH agonists	Based on OI or OS regimen used
Pulsatile GnRH therapy, used for ovulation induction in patients with hypothalamic amenorrhea			
GnRH therapy	75 ng/kg (Discontinued after ovulation)	Injection site adverse effects; multiple gestation (4%−8%[53]); ovarian hyperstimulation (<1%[54])	Pregnancy rates 70%−100% after up to 6 mo[48]
Dopamine agonists, for treatment of hyperprolactinemic anovulation (titrated to normalize serum prolactin levels) [c]			
Bromocriptine (Parlodel)	Starting at 1.25mg orally daily	Dizziness (25%), headache (25%−30%), nausea/vomiting (30%−50%)	52%−72% Resumption of ovulatory cycles[55]
Cabergoline (Dostinex)	Starting at 0.25 mg orally twice weekly; may be given vaginally to minimize adverse effects		
Progesterone			
Crinone 8% vaginal gel	Gel: 90 mg intravaginal daily	Abdominal discomfort (15%), headache (13%), vaginal discharge (7%), nausea (22%)	
Endometrin, 100-mg vaginal tablet	Tablet: 100 mg intravaginal 2–3 times daily		
Intramuscular progesterone in oil	Injection: 50 mg daily		

Abbreviations: GnRH, gonadotropin-releasing hormone; IUI, intrauterine insemination; IVF, in vitro fertilization; LBR, live birth rate; LH, luteinizing hormone; OI, ovulation induction; OS, ovarian stimulation; PCOS, polycystic ovary syndrome.

[a] The medications may be used alone or in combination in a fertility treatment cycle.

[b] Higher doses (200–250 mg daily have been used in women refractory to these doses, but these doses exceed US Food and Drug Administration recommendation.

[c]

The Potential of Reproductive Medicine

Emerging reproductive technologies have the potential to change evaluation and treatment of infertility. Advances in DNA sequencing have generated large data sets that may prove useful in developing personalized treatments. The development of artificial gametes generated in vitro has resulted in live births in animal models, although no study has reported the birth of human offspring from artificial gametes. The use of gene therapies to improve oocyte quality, such as autologous mitochondrial transfer into oocytes, has been explored in prospective cohort studies,[96,97] although prognosis was not improved in a randomized pilot study of women who had previously unsuccessful IVF.[98] Lack of rigorous testing, as well as ethical concerns including informed consent from future biological children, long-term safety, and questions about natural limits to the reproductive lifespan and the demands of later-life child-rearing, remains a major barrier to widespread use and should be at the forefront of discussions surrounding these innovations. Caution is warranted in implementing fertility treatments that have not been rigorously tested, have insufficient evidence to suggest efficacy, or for which evidence of benefit is extrapolated from unrelated populations. Approximately 1 in 8 women aged 15 to 49 years receive infertility services. Although success rates vary by age and diagnosis, accurate diagnosis and effective therapy along with shared decision-making can facilitate achievement of fertility goals in many couples treated for infertility.

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