Female Infertility

Details

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Continuing Education Activity

Female infertility, defined as the inability to achieve pregnancy after 12 months of unprotected intercourse in women younger than 35 or 6 months in women 35 or older, remains a major global health concern affecting nearly 15% of couples. This activity reviews the female factors that contribute to about half of all infertility cases, stemming from ovulatory dysfunction, tubal or uterine abnormalities, endometriosis, genetic disorders, and lifestyle influences, as well as advances in diagnostic techniques, hormonal assays, imaging modalities, and assisted reproductive technologies that have improved outcomes, though disparities in access, cost, and emotional burden persist. Participants will gain an understanding of the complex etiology and evidence-based management strategies that enable clinicians to optimize care and enhance fertility outcomes.

This course explores the evidence-based management of female infertility, emphasizing underlying etiologies, diagnostic studies, treatment strategies, and emerging reproductive technologies. This activity for healthcare professionals is designed to enhance the learner's competence in identifying the physiologic mechanisms of female infertility, performing the recommended evaluation, applying individualized treatment approaches, and implementing an appropriate interprofessional approach when managing this condition to enhance patient outcomes and support emotional well-being.

Objectives:

- Identify the pathophysiologic mechanisms contributing to female infertility.
- Apply evidence-based diagnostic strategies, including hormonal, imaging, and genetic assessments, to determine underlying causes of infertility.
- Implement individualized, patient-centered treatment plans that integrate lifestyle, metabolic, and psychosocial considerations.
- Collaborate with interprofessional teams when managing female infertility to optimize care coordination and enhance reproductive outcomes.

Introduction

Female infertility, defined as the inability to achieve pregnancy after 12 months of regular, unprotected sexual intercourse in women younger than 35 or after 6 months in women older than 35, represents a major global health concern.[1] Approximately 85% of couples conceive within the first 12 months of adequate, unprotected intercourse, with about 30% to 40% achieving pregnancy within the first 3 months. The lower range reflects real-world factors within the general population, including age, undiagnosed infertility in either partner, lifestyle influences such as obesity and smoking, and subclinical medical conditions that collectively diminish overall fecundability. Population-based studies indicate an average monthly conception probability of 15% to 20%, resulting in a cumulative pregnancy rate of approximately 30% to 40% after 3 months.[2][3]

Approximately 15% of couples worldwide experience infertility, with female factors accounting for about 50% of cases, male factors for 40%, and combined etiologies responsible for the remainder.[4][5] Female infertility carries profound psychological, social, and medical implications that require a comprehensive understanding and management. Advances in assisted reproductive technologies (ART), including in vitro fertilization (IVF), have significantly transformed clinical approaches, although disparities in access, complex underlying causes, financial constraints, and emotional distress continue to pose challenges.[6]

Infertility extends its impact beyond physiological mechanisms, affecting mental health, interpersonal relationships, and social identity. In high-income nations, delayed childbearing driven by career or financial priorities contributes to higher infertility rates, whereas in low-resource regions, infectious diseases remain predominant causes.[7] The psychological burden, often marked by anxiety and depression, reinforces the importance of holistic, interprofessional care.[8]

Etiology

Female infertility results from multiple interacting causes that often overlap in complex ways (see **Table 1**). Ovulatory dysfunction represents one of the major categories, accounting for 25% to 40% of cases, with polycystic ovarian syndrome (PCOS) responsible for approximately 70% of anovulatory states.[9] Additional contributors to ovulatory dysfunction include hypothalamic-pituitary disorders, eg, functional hypothalamic amenorrhea, hyperprolactinemia resulting from pituitary adenoma, and primary ovarian insufficiency, also known as premature ovarian failure.[10]

Tubal factors contribute to 20% to 35% of female infertility cases and commonly result from obstruction or dysfunction of the fallopian tubes due to pelvic inflammatory disease (PID), endometriosis, or previous pelvic surgery.[11] Uterine factors, including leiomyomas, endometrial polyps, Asherman syndrome, and congenital anomalies, eg, a septate uterus, account for 10% to 15% of cases.[11] Endometriosis, characterized by ectopic endometrial tissue that promotes inflammation and adhesion formation, represents another 10% to 15% of female infertility cases.[12][13]

The revised American Society for Reproductive Medicine (ASRM) classification system (r-ASRM) categorizes endometriosis into 4 stages based on the extent, location, and depth of lesions, as well as the presence of adhesions and ovarian involvement. The scoring system defines stage I as minimal (1–5 points), stage II as mild (6–15 points), stage III as moderate (16–40 points), and stage IV as severe (>40 points).[13][14]

Approximately 15% to 30% of female infertility cases remain unexplained despite thorough evaluation and complete diagnostic workup.[15] Additional contributing factors include lifestyle and environmental influences such as obesity, smoking, alcohol consumption, and exposure to endocrine-disrupting chemicals, each exerting variable effects on reproductive function.[16] Genetic and chromosomal abnormalities, including Turner syndrome, fragile X premutation, and structural translocations, also play a role in the development of female infertility.[17]

Table 1. Common Causes of Female Infertility

Infertility Mechanism	Prevalence	Clinical Features	Associated Etiologies
Ovulatory Dysfunction	25%–40%	• Anovulation • Irregular cycles	• PCOS • Hypothalamic amenorrhea • Primary ovarian insufficiency
Tubal Factor	20%–35%	• Tubal obstruction • Hydrosalpinx	• PID • Endometriosis • Prior surgery
Uterine Factor	10%–15%	• Abnormal cavity • Implantation failure	• Leiomyomas • Asherman syndrome • Septate uterus
Endometriosis	10%–15%	• Pelvic adhesions • Inflammation	• Pelvic pain • Endometriomas
Unexplained Infertility	15%–30%	• No identifiable cause	• Subclinical oocyte • Immune issues

Epidemiology

Globally, infertility affects 48.5 million couples, with female infertility impacting 8.8% of women in the United States between the ages of 15 and 49 (see **Table 2**).[18][19] The World Health Organization (WHO) estimates a 15% prevalence among reproductive-age couples, with notable regional variation.[4] In high-income countries, delayed childbearing remains a major contributor, as fertility declines after age 35.[3] The average age of first-time mothers in the United States increased from 24.9 in 2000 to 27.3 in 2020, corresponding with a 20% rise in infertility treatment demand.[20] In low-income and middle-income regions, untreated sexually transmitted infections (STIs) leading to PID represent a key cause, with Sub-Saharan Africa reporting infertility rates between 20% and 30%.[21] In South Asia, early marriage and frequent pregnancies heighten the risk of uterine and tubal injury.[7]

Racial and ethnic disparities further influence infertility outcomes. Black women in the United States experience a 1.5-fold higher infertility risk and lower access to ART, with 8% utilization compared to 12% among White women.[22] Hispanic and Native American women also face higher infertility prevalence, often linked to socioeconomic barriers and comorbid health conditions.[23] Economic limitations compound these inequities, as in vitro fertilization (IVF) costs approximately 20,000 dollars per cycle, while only 15 of 50 US states mandate insurance coverage.[24] Globally, ART remains inaccessible for most couples, with only 1% to 2% of infertile couples in low-resource settings receiving treatment.[6] Environmental exposures further contribute, with air pollution increasing infertility risk by roughly 10%, and women residing near high-traffic roads facing greater vulnerability.[25]

The optimal reproductive age, balancing biological, medical, and social factors, generally spans 20 to 35 years, with peak fertility occurring during the early to mid-twenties.[2][3] Monthly conception probability reaches 25% to 30% in the early twenties.[2] Both oocyte quantity and quality decline gradually after age 30, with a pronounced decrease after 35, when aneuploidy rates rise from 20% to 60% by age 40, diminishing embryo viability.[26] Miscarriage risk also escalates with age, increasing from 10% between ages 20 and 24 to 50% between ages 40 and 44.[3] Women aged 20 to 35 generally experience lower risks of gestational diabetes, preeclampsia, and preterm birth compared with those older than 35.[3] Maternal and neonatal outcomes remain most favorable within this age range, with reduced need for obstetric interventions.[20]

Antimüllerian hormone (AMH) levels and antral follicle counts reach their highest values in the twenties, reflecting strong ovarian reserve that supports both natural conception and favorable assisted reproductive outcomes.[27][28] The 20-to-35 age range often coincides with optimal physical health, emotional maturity, and growing financial stability, although social and cultural factors influence individual timing decisions. Delayed childbearing beyond age 35 has become increasingly common due to career goals and economic considerations, contributing to a 20% increase in infertility treatment demand.[20]

Table 2. Global Infertility Prevalence and Contributing Factors

Region	Infertility Prevalence	Contributing Factors	Risk of Infertility
North America	8%–12%	Delayed childbearing, obesity	10%–12%
Sub-Saharan Africa	20%–30%	STIs, PID, and limited healthcare	1%–2%
South Asia	15%–20%	Early marriage, frequent pregnancies	2%–5%
Europe	10%–15%	Delayed childbearing and environmental toxins	8%–10%

Pathophysiology

The underlying pathophysiological mechanisms of female infertility include disruptions in ovulation, oocyte transport, fertilization, or implantation, with abnormalities varying according to the specific etiology (see **Table 3**).

Ovulatory Dysfunction

Ovulatory dysfunction, particularly in PCOS, arises from hyperandrogenism and insulin resistance, which impair follicular development. Elevated luteinizing hormone (LH)-to-follicle-stimulating hormone (FSH) ratios contribute to anovulation.[29] Hypothalamic amenorrhea suppresses gonadotropin-releasing hormone (GnRH) pulsatility, leading to decreased FSH and LH secretion.[10] Hyperprolactinemia inhibits GnRH release, promoting follicular atresia through reduced granulosa cell proliferation and increased apoptosis in developing follicles, often due to genetic or autoimmune mechanisms.[30] Hypothyroidism further decreases ovulation rates by 20% through disrupted gonadotropin regulation.[31]

Oocyte Transport

PID causes tubal scarring, hydrosalpinx, or both, which compromise ciliary motility and oocyte transport. *Chlamydia trachomatis* infection represents the most common cause of hydrosalpinx.[13][32] Cytokines within hydrosalpinx fluid, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), reduce implantation success by approximately 50%.[13] Around 15% of untreated *Chlamydia* infections progress to fallopian tube fibrosis through epithelial–mesenchymal transition mediated by myofibroblast activation under the influence of transforming growth factor-beta (TGF-β), TGF-β receptor 1, connective tissue growth factor (CTGF), and nuclear factor of activated T-cells. The resulting extracellular matrix protein accumulation promotes endometrial fibrosis and tubal occlusion.[32][33]

Tubal Factor Infertility

Endometriosis contributes to tubal factor infertility through pelvic adhesions, distorted anatomy, and chronic inflammation mediated by cytokines, eg, interleukin-1β (IL-1β) and interleukin-8 (IL-8).[34] Endometriomas lower AMH levels by 30% to 40%, reflecting a reduction in ovarian reserve.[34] Adhesions and inflammatory cytokines also impair oocyte quality and implantation potential.[34]

Uterine Factors

Uterine factors encompass submucosal leiomyomas, Asherman syndrome, and congenital anomalies (eg, septate or bicornuate uterus). Submucosal leiomyomas distort the endometrial cavity, diminishing vascularity and endometrial receptivity.[35] Asherman syndrome causes intrauterine fibrosis, reducing pregnancy rates by approximately 70%.[36] A septate uterus increases miscarriage risk due to inadequate vascular supply and poor implantation conditions.[36]

Subclinical Abnormalities

Subclinical abnormalities, including diminished ovarian reserve and altered integrin expression, account for roughly 20% of infertility cases classified as unexplained.[37] Age-related decline in fertility results from rising oocyte aneuploidy, which increases from 20% at age 30 to 60% at age 40, with mitochondrial dysfunction contributing to poor embryo development.[38] Telomere shortening and oxidative stress, caused by reactive oxygen species, further accelerate oocyte aging.[39] Obesity disrupts the hypothalamic–pituitary–ovarian axis function by elevating leptin levels and lowering adiponectin levels, thereby impairing ovulation.[40] Environmental exposures, including phthalates and particulate matter, reduce oocyte yield by approximately 15% and fertility by 10%, respectively.[25][41]

Table 3. Pathophysiological Mechanisms by Etiology

Etiology	Pathophysiological Mechanisms	Findings	Effects
PCOS	Hyperandrogenism, insulin resistance	Elevated LH, insulin	Anovulation, poor oocyte quality
Tubal Factor	Scarring, hydrosalpinx	IL-6, TNF-α, TGF-β	Impaired oocyte transport
Endometriosis	Inflammation, adhesions	IL-1β, IL-8, oxidative stress	Reduced implantation, oocyte damage
Uterine Factor	Cavity distortion, fibrosis	Reduced vascularity, integrins	Implantation failure, miscarriage
Age-Related Decline	Aneuploidy, mitochondrial dysfunction	Telomere shortening, reactive oxygen species	Poor embryo viability

History and Physical

A comprehensive history and physical examination provides the foundation for the diagnostic evaluation of female infertility.

Clinical History

Detailed menstrual history offers critical insight, as irregular cycles with more than a 7-day variation suggest ovulatory dysfunction, while amenorrhea indicates hypothalamic dysfunction or primary ovarian insufficiency.[33] Oligomenorrhea occurs in approximately 80% of women with polycystic ovary syndrome (PCOS).[9] Reproductive history, including prior pregnancies, miscarriages, or ectopic pregnancies, can reveal uterine or tubal pathology.[42] Medical and surgical histories, particularly involving diabetes, thyroid disease, or pelvic surgery, may also compromise fertility.[43] Lifestyle factors exert substantial influence, with smoking reducing fertility by 30% and alcohol intake exceeding 14 units per week doubling infertility risk.[16] Body mass index (BMI) and occupational exposures further affect reproductive potential.[44]

Symptoms guide targeted evaluation. Pelvic pain or dyspareunia may indicate endometriosis or PID, galactorrhea suggests hyperprolactinemia, and male-pattern hair growth, including facial hair, may signal PCOS.[45] Family history of early menopause or genetic disorders increases the likelihood of primary ovarian insufficiency.[46]

Physical Examination

Physical examination includes assessment for hyperandrogenism signs such as hirsutism, acne, obesity, and acanthosis nigricans, which may reflect insulin resistance or PCOS, while a body mass index (BMI) below 18.5 kg/m^2 can indicate hypothalamic amenorrhea.[40][47] Pelvic examination may identify uterine or adnexal abnormalities, including leiomyomas or endometriomas.[48] Evaluation of secondary sexual characteristics can reveal poor breast development, suggesting hypogonadism.[49] Thyroid assessment may detect nodules indicative of thyroid dysfunction, a condition affecting approximately 10% of infertile women.[30] Additional physical features, eg, short stature, low hairline, webbed neck, widely spaced nipples, or cubitus valgus, may be suggestive of chromosomal abnormalities, including Turner syndrome.[50]

Evaluation

The diagnostic evaluation of female infertility primarily involves studies to help identify the underlying etiology, including ovulatory, tubal, and uterine dysfunctions (see **Table 4**).

Ovulatory Assessments

Studies to evaluate ovulatory function include measuring serum progesterone at a mid-luteal level greater than 3 ng/mL, which confirms ovulation.[33] A mid-cycle rise of at least 0.5 °F in basal body temperature is suggestive of a progesterone level surge, which may be indicative of ovulation, although this is variable.[51] Ovulation predictor kits are available over-the-counter and detect the LH surge with an accuracy of approximately 97% and an ovulation prediction sensitivity and specificity of 100% and 25%, respectively.[52][53][43][53]

Furthermore, ovarian reserve testing is achievable by measuring the AMH level. A level of less than 1 ng/mL indicates low reserve, while a level of greater than 4 ng/mL suggests PCOS; a level between 1 ng/mL and 3.5 ng/mL indicates normal follicular function.[54] Antral follicle count involves counting the ovarian follicles of 9 mm or less, usually measured by transvaginal ultrasound, with a count of less than 5 follicles indicating low reserve, a count of 5 to 20 indicating normal follicular reserve, and a count of greater than 20 may suggest PCOS.[28] Day 3 FSH and estradiol measurement is useful for determining ovarian reserve because the feedback engendered by functional ovaries controls the release of FSH, with levels in women of reproductive age typically 3 to 9 mIU/mL, though this can vary slightly depending on the laboratory assay used, with higher values (>10 mIU/mL) indicating diminished ovarian reserve and lower values (<3 mIU/mL) potentially suggesting hypothalamic-pituitary dysfunction.[54]

Tubal Function Assessments

Tubal patency can be assessed by hysterosalpingography (HSG) with 85% to 90% sensitivity for obstruction.[55] HSG is associated with increased pregnancy and live birth rates, especially with oil-soluble media, compared to controls (OR 2.98; 95% CI 1.05-6.37).[56] Hysterosalpingo-contrast sonography (HyCoSy) has 80% concordance with HSG and is a reliable alternative to HSG with less invasiveness.[57] Laparoscopy is the gold standard investigation for endometriosis.[58]

Uterine Assessment

Uterine evaluation relies primarily on imaging and direct visualization techniques to identify structural abnormalities. Transvaginal ultrasound (TVUS) has a sensitivity of approximately 90% in detecting fibroids, providing a first-line, noninvasive assessment of uterine anatomy.[48] Sonohysterography enhances visualization of the endometrial cavity, achieving about 95% sensitivity for identifying polyps.[59] Hysteroscopy serves both diagnostic and therapeutic purposes, enabling direct inspection and management of intrauterine pathologies that contribute to infertility.[60] Magnetic resonance imaging (MRI) offers the highest diagnostic precision, with 98% accuracy in detecting congenital and acquired uterine anomalies.[59]

Endocrine Studies

Endocrine evaluation involves targeted hormonal and metabolic testing to identify systemic contributors to infertility. A thyroid-stimulating hormone (TSH) level above 4 mIU/L suggests hypothyroidism, which doubles infertility risk through altered gonadotropin dynamics and ovulatory dysfunction.[31] Prolactin levels exceeding 25 ng/mL indicate hyperprolactinemia, a frequent cause of anovulation.[61] Elevated serum androgens or glucose levels support a diagnosis of PCOS.[29] An elevated 17-hydroxyprogesterone level suggests congenital adrenal hyperplasia.[62] Genetic evaluation, including karyotyping or fragile X premutation testing, assists in identifying the underlying cause of primary ovarian insufficiency.[49]

Because approximately 40% of infertility cases involve a male factor, semen analysis remains a critical component of the initial workup. A normal semen analysis effectively excludes male infertility, allowing clinicians to focus on more extensive and costlier investigations of female reproductive factors.[5]

Table 4. Diagnostic Tests for Female Infertility

Test	Purpose	Sensitivity/Specificity	Findings
Serum Progesterone	Confirm ovulation	90%/85%	>3 ng/mL mid-luteal phase confirms ovulation
Antimüllerian Hormone	Assess ovarian reserve	80%/90%	<1 ng/mL signifies low reserve
Hysterosalpingography	Evaluate tubal patency	85%–90%/80%	Contrast spill signifies patent tubes
Hysteroscopy	Diagnose intrauterine pathology	95%/90%	Polyps, adhesions, septa
Thyroid Function	Detect hypothyroidism	95%/95%	TSH >4 mIU/L suggests hypothyroidism

Treatment / Management

Treatment of female infertility requires an individualized approach that balances efficacy, risk, and patient preference (see **Table 6**). Management strategies depend on the underlying etiology, with varying success rates across different interventions (see **Table 5**).

Pharmacologic Management

Ovulatory dysfunction responds favorably to pharmacologic therapy. Clomiphene citrate induces ovulation in approximately 80% of women, achieving a 40% pregnancy rate per cycle.[63] Adverse effects include hot flashes in 10% of cases, multiple gestations in 8%, and OHSS.[64] Letrozole demonstrates superiority over clomiphene citrate in managing PCOS, offering higher ovulation, pregnancy, and live birth rates (27.5% versus 19.1%), improved endometrial thickness, greater monofollicular development, and a reduced multiple pregnancy rate (3% versus 5%).[63][65][66][67]

Gonadotropin therapy with recombinant FSH, LH, and human chorionic gonadotropin (hCG) achieves ovulation in 90% of patients but carries a 1% to 6% risk of OHSS.[68] Metformin enhances ovulation in PCOS by improving insulin sensitivity and increases pregnancy rates by 15% when used in combination with clomiphene.[69] Dopamine agonists such as cabergoline and bromocriptine restore ovulation in 80% to 90% of women with hyperprolactinemia.[70] Lifestyle modification, including 5% to 10% weight loss, restores ovulation in 50% to 60% of obese women with PCOS.[71] Antibiotic therapy benefits patients with pelvic inflammatory disease (PID) by preventing additional tubal injury.[72]

In Vitro Fertilization and Intrauterine Insemination

Management of tubal factor infertility depends on the extent of tubal damage. IVF offers the best outcomes for women with severe tubal disease, achieving live birth rates of 40% to 50% per cycle in those younger than 35.[73] Salpingectomy in patients with hydrosalpinx increases IVF success by 20% by eliminating inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) that leak into the uterine cavity and impair implantation.[74][75][76][77] The procedure also lowers the risk of post-IVF ectopic pregnancy. Tubal reanastomosis yields pregnancy rates of 60% to 80% in women with mild to moderate tubal damage, while fimbrioplasty improves conception rates by 20% to 40%.[78]

Unexplained infertility, diagnosed after a comprehensive evaluation of both partners, often responds to intrauterine insemination (IUI) with ovulation induction, which achieves pregnancy rates of 10% to 15% per cycle. IVF yields higher success, with 30% to 40% pregnancy rates.[79][80][81] Conservative management can result in spontaneous conception in 20% to 30% of women younger than 35.[82]

Surgical Management

Uterine factors often respond to surgical correction. Hysteroscopic surgery improves pregnancy rates by 50% to 70%.[83] Myomectomy enhances implantation by 30%, while septum resection in women with a septate uterus reduces miscarriage rates from 80% to 20%.[35][36]

Endometriosis-related infertility requires a tailored approach. Hormonal suppression alleviates symptoms but does not improve fertility outcomes.[48] Laparoscopic excision of endometriotic lesions enhances pregnancy rates by approximately 50% in stage I and II disease, while IVF provides a 30% to 40% success rate in advanced stages.[84][85]

Adjunct Therapies

Adjunctive measures enhance overall fertility outcomes. Weight optimization improves conception rates by 20% to 30%, while smoking and alcohol cessation increase IVF success by 15%.[86][87] Acupuncture may enhance IVF outcomes by 10%, and antioxidant therapy, including coenzyme Q10, improves oocyte quality by 5% to 10%.[79][88]

Advanced Therapies

Advancements in ART continue to refine infertility management. IVF protocols incorporating antagonist regimens reduce OHSS risk, while preimplantation genetic testing improves live birth rates by 20% in women older than 37.[8][80] Frozen embryo transfer yields approximately 10% higher success than fresh transfer, and donor oocyte utilization achieves live birth rates of 50% to 60%.[89]

Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) represent earlier ART developed for nontubal infertility, including unexplained infertility, mild male factor, or cervical issues. These procedures require laparoscopic placement of gametes or zygotes into patent fallopian tubes under general anesthesia, restricting use to fewer than 1% of ART cycles today. In GIFT, retrieved oocytes are combined with sperm and transferred immediately into the tubes. Success rates reach 20% to 30% per cycle, with live birth rates around 25% in women under 35. Associated complications include surgical risks such as infection or bleeding (1%–2%), multiple gestations (15%–20%), and ectopic pregnancy (5%–7%).

ZIFT involves laboratory fertilization of oocytes followed by transfer of zygotes into the fallopian tubes the following day. Pregnancy rates range from 25% to 35%, with live birth rates near 30% in women under 35. Complications mirror those of GIFT and include ectopic pregnancy (4%–6%).[3][90] Despite their early promise, GIFT and ZIFT have largely been replaced by IVF due to greater invasiveness, surgical risk, and lower efficiency. IVF achieves higher live birth rates (40%–50%) with fewer ectopic pregnancies (1.3%) and avoids the need for laparoscopy. These procedures remain options for select cases, eg, failed IUI or mild endometriosis, or for patients with religious or ethical concerns regarding in vitro fertilization, although current guidelines consistently favor IVF.[3][16]

In Vitro Fertilization Overview

IVF is a cornerstone of assisted reproductive technology ART for managing female infertility, particularly in cases of ovulatory dysfunction, tubal factor, endometriosis, diminished ovarian reserve, or unexplained infertility. IVF involves controlled ovarian stimulation, oocyte retrieval, laboratory fertilization, and embryo transfer. Current guidelines provide recommendations regarding the procedure, medications, doses, timing, prognosis, success rates, and complications.[3][16][85][91][92][93]

IVF is a multistep process typically spanning 4 to 6 weeks per cycle, including:

1. **Ovarian stimulation**: The ovaries are stimulated to produce multiple follicles using injectable hormones. This step aims to retrieve 8 to 15 mature oocytes for optimal success.[3][16]
2. **Oocyte retrieval**: Performed under ultrasound guidance 34 to 36 hours after a trigger injection. A transvaginal needle aspirates follicles; the procedure lasts 15 to 30 minutes under sedation.[3]

3. **Fertilization**: Oocytes are mixed with sperm in a lab (conventional IVF) or injected with a single sperm (intracytoplasmic sperm injection for male factor or poor oocyte quality).[3][91]
4. **Embryo culture**: Embryos are cultured for 3 to 5 days. Day 3 embryos (in the cleavage stage) have 6 to 8 cells; day 5 embryos, each containing 100 to 200 cells (blastocysts), are more advanced and preferred for transfer to reduce the risk of multiple pregnancies.[16][93]
5. **Embryo transfer**: 1 to 2 embryos are placed in the uterus via a catheter. Fresh transfer occurs immediately; frozen embryo transfer uses cryopreserved embryos in a subsequent cycle.[92][93]
6. **Luteal support**: Progesterone supplementation supports implantation until placental hormone production takes over (around week 8–10 of pregnancy).[3]
7. **Pregnancy test**: Blood hCG test performed 10 to 14 days posttransfer.
8. **Monitoring**: Ultrasound and estradiol studies are performed every 2 to 3 days; retrieval is performed when follicles are 18 mm or larger.[3][94]

Preimplantation genetic testing may be added for aneuploidy screening or monogenic disorders, involving embryo biopsy on day 5.[3][85]

Hormone protocols of IVF

IVF protocols vary in approach, including long agonist, antagonist, and flare regimens, with antagonist protocols commonly preferred to prevent premature LH surge and reduce the risk of OHSS. Gonadotropins, eg, follitropin alfa (Gonal-F) or follitropin beta (Puregon), are administered at 150 to 450 IU/day subcutaneously for 8 to 14 days, beginning on day 2 to 3 of the cycle to stimulate follicular growth. Menotropins (Menopur), which combine FSH and LH, are often used at comparable doses for poor responders.[67]

GnRH antagonists (eg, ganirelix or cetrorelix at 0.25 mg/day subcutaneously) are introduced from day 5 to 6 of stimulation until ovulation triggering to prevent premature LH surge.[3][75] In contrast, long protocols employ GnRH agonists like leuprolide 0.5 to 1 mg/day subcutaneously for 2 to 3 weeks before stimulation to achieve pituitary downregulation.[3][75]

Oocyte maturation is triggered with either hCG (Ovidrel 250 µg subcutaneously) or a GnRH agonist (eg, leuprolide 1–2 mg subcutaneously), administered 36 hours before retrieval.[94] Luteal phase support follows retrieval, typically with progesterone (Crinone gel 90 mg vaginally once daily or Utrogestan 200 mg orally 3 times daily) until pregnancy confirmation. Ultrasound and estradiol monitoring every 2 to 3 days during stimulation guide timing for retrieval, which occurs when leading follicles reach at least 18 mm in diameter.[3]

Prognosis and success rates

Prognosis and success rates depend on maternal age, underlying cause of infertility, ovarian reserve, embryo quality, and lifestyle factors. Outcomes are commonly reported as live birth rate per cycle or per embryo transfer. The overall live birth rate ranges from 20.7% to 50% per cycle, decreasing with age, from 48.5% in women younger than 35 to 11% in those older than 43, according to data from the Centers for Disease Control (CDC).[16][92] Cumulative live birth rate after 3 cycles approximates 60% to 70% in women under 35, though lower rates occur in patients with diminished ovarian reserve or advanced age.[16][85]

Prognosis improves with blastocyst transfer, preimplantation genetic testing for aneuploidy, which enhances outcomes by approximately 20% in women older than 37, and frozen embryo transfer, which offers a 10% higher success rate compared to fresh transfer. Single embryo transfer reduces multiple gestations while maintaining success rates.[92][93] Mild stimulation or mini-IVF protocols, using lower gonadotropin doses (75–150 IU FSH), yield live birth rates of approximately 30% to 40% in women under 35 and suit poor responders or those seeking to minimize OHSS risk.[3][85]

In vitro maturation

In some selected patients, like patients with estrogen-sensitive cancers or patients at high risk for OHSS in whom conventional IVF may be contraindicated, in vitro maturation (IVM) is a modified form of IVF that may be a better alternative for such candidates. IVM involves retrieving immature oocytes from the ovaries, maturing them in a laboratory, and then using them for fertilization, typically without or with minimal ovarian stimulation with a course of FSH plus or minus hCG, making it distinct from standard IVF. Such immature follicles are then cultured to maturation before fertilization. Success rates of IVM are lower than those of IVF.[3][95]

Table 5. Treatment Options and Success Rates

Therapy	Infertility Factor	Success Rates	Complications
Clomiphene Citrate	Anovulation	40% pregnancy/cycle	Multiples (8%), hot flashes
Letrozole	PCOS	27.5% live birth	Multiples (3%–5%)
IVF	Tubal factor, endometriosis, unexplained	40%–50% live birth (<35)	OHSS (1%–6%), multiples (20%–30%)
Hysteroscopic Surgery	Uterine pathology	50%–70% improved pregnancy	Bleeding (<1%), infection (1%)

Laparoscopy	Endometriosis	50% pregnancy (stage I–II)	Ovarian reserve loss (20%)

Table 6. Quick Guide for Management of the Common Infertility Causes

Infertility Mechanism	Etiologies	Prevalence	Evaluation	Management

Ovulatory Dysfunction	• PCOS 70% of cases
	• Hypothalamic amenorrhea
	• Hyperprolactinemia
	• Premature ovarian insufficiency
	• Thyroid dysfunction [9][10][11]
		25%–40% [9]	• History: Irregular cycles, amenorrhea
			• Tests
			  • Serum progesterone (<3 ng/mL = anovulation)
			  • AMH (>4 ng/mL suggests PCOS) [27]
			  • Day 3 FSH/estradiol
			  • Thyroid function (TSH >4 mIU/L) [31]
			  • Prolactin (>25 ng/mL) [61]
				• PCOS: Letrozole (2.5–7.5 mg/day, 27.5% live birth rate) [66]
				• Hypothalamic amenorrhea: Weight gain (BMI >19) [86]
				• Hyperprolactinemia: Cabergoline (0.5 mg twice weekly) [70]

Tubal Factor	• PID
	• Endometriosis
	• Prior pelvic surgery
	• Salpingitis isthmica nodosa
	• Hydrosalpinx [11][12]
		20%-35% [11]	• History: PID, ectopic pregnancy, pelvic surgery
			• Studies
			  • Hysterosalpingography (HSG, 85%–90% sensitivity) [55]
			  • Laparoscopy for complex cases [58]
				• IVF (40–50% live birth rate in women younger than 35
				• Salpingectomy improves success by 20%) [73][77]

Uterine Factor	• Leiomyomas (submucosal)
	• Endometrial polyps
	• Asherman syndrome
	• Congenital anomalies (eg, septate uterus) [12][13]
		10%-15% [12]	• History: Heavy periods, prior uterine surgery
			• Tests
			  • Transvaginal ultrasound (90% sensitivity for fibroids) [48]
			  • Sonohysterography (95% for polyps) [59]
			  • Hysteroscopy (gold standard) [60]
				• Hysteroscopic surgery (eg, adhesiolysis for Asherman syndrome, septum resection; 50%–70% improved pregnancy rates) [83]

Endometriosis	• Ectopic endometrial tissue
	• Endometriomas
	• Pelvic adhesions [13][14][15]
		10%-15% [13]	• History: Dysmenorrhea, dyspareunia
			• Tests
			  • Laparoscopy (gold standard)
			  • Ultrasound for endometriomas [58][48]
				• Laparoscopic excision (50% spontaneous pregnancy rate in stage I–II)
				• IVF (30%–40% success in advanced disease) [85]

Unexplained Infertility	• Subclinical oocyte quality issues • Immunological factors • Endometrial receptivity defects [15][18]	15%-30% [15]	• History: Diagnosis of exclusion (normal ovulation, tubal patency, uterine cavity, semen analysis) • Tests: complete workup, including AMH, antral follicle count, HSG [27][28][55]	• IUI with ovulation induction (clomiphene/letrozole, 10%–15% pregnancy rate per cycle) • IVF (30%–40% in women older than 38) [81]

Lifestyle/Environmental Factors	• Obesity (BMI >30)
	• Smoking
	• Excessive alcohol (>14 units/week)
	• Endocrine-disrupting chemicals (eg, phthalates, bisphenol A) [3][16][19]
		Variable [16]	• History: BMI (>30 or <18.5), smoking, alcohol, and environmental exposures
			• Tests: BMI measurement, toxin exposure history
				• Lifestyle modification
				  • Weight optimization (5%–10% loss, 50%–60% ovulation restoration in obese PCOS) [71]
				  • Smoking/alcohol cessation (15% improved IVF success) [87]

Genetic/Chromosomal	• Turner syndrome
	• Fragile X premutation
	• Balanced translocations [3][17]
		<5% [17]	• History: Recurrent pregnancy loss, early menopause
			• Tests
			  • Karyotyping
			  • Fragile X premutation (10% of premature ovarian insufficiency cases) [49]
				• IVF with preimplantation genetic testing (20% improved live birth rate in women >37) [8]
				• Donor oocytes (50% to 60% live birth rate in premature ovarian insufficiency) [89]

Differential Diagnosis

The differential diagnosis of female infertility encompasses a broad range of conditions that can disrupt the reproductive process. These conditions are categorized by their primary mechanism or the reproductive stage affected, ensuring clarity. Each of the major causes of female infertility shall be analyzed to identify conditions that can mimic them and should be differentiated.

Polycystic Ovarian Syndrome

PCOS represents a prevalent endocrine disorder marked by hyperandrogenism—manifesting as hirsutism and acne—alongside ovulatory dysfunction with irregular or absent menstrual cycles and polycystic ovarian morphology on ultrasound. PCOS accounts for approximately 70% of anovulatory infertility, disrupting ovulation through insulin resistance and elevated LH-to-FSH ratios.[5] Diagnostic indicators include menstrual irregularity, clinical or biochemical evidence of hyperandrogenism, AMH levels exceeding 4 ng/mL, and ultrasound findings of at least 12 follicles per ovary.[5] Differential diagnoses encompass androgen-secreting ovarian tumors, adrenal tumors, nonclassic congenital adrenal hyperplasia (which presents with elevated 17-hydroxyprogesterone, hyperandrogenism, irregular cycles, and family history), Cushing syndrome, prolactinoma, and thyroid dysfunction.[75]

Among women of reproductive age, normal total testosterone ranges from 8 to 60 ng/dL, while free testosterone typically measures between 0.3 and 1.9 ng/dL.[62][90] Androgen-producing ovarian tumors generally present with total testosterone levels above 150 ng/dL.[62] Adrenal tumors can be distinguished by markedly elevated DHEA-S levels, typically greater than 500 to 700 µg/dL.[90] A fasting 17-hydroxyprogesterone concentration above 200 ng/dL during the follicular phase suggests nonclassic CAH, confirmed when ACTH stimulation raises the value above 500 ng/dL.[75][95] Cushing syndrome manifests through hypercortisolism, weight gain, and hypertension, while prolactinoma often produces prolactin levels exceeding 25 ng/mL, accompanied by anovulation; persistent elevation requires pituitary MRI to exclude adenoma.[61] A TSH level above 4 mIU/L reflects hypothyroidism, which disrupts ovulation, and even subclinical hypothyroidism doubles the risk of infertility.[30][31]

Endometriosis

Endometriosis often presents with pelvic pain, dysmenorrhea, dyspareunia, or endometriomas on ultrasound, with lesions confirmed by laparoscopy serving as key diagnostic indicators in addition to its strong association with infertility.[9] Differential diagnoses include PID, adenomyosis—marked by the presence of endometrial tissue within the myometrium—leiomyomas, ovarian cysts, ovarian torsion, interstitial

cystitis or painful bladder syndrome, irritable bowel syndrome (IBS), and pelvic congestion syndrome. Although several of these conditions can also contribute to infertility, they typically do so to a lesser extent than endometriosis. Distinguishing these disorders requires a detailed clinical history, thorough physical examination, and appropriate diagnostic imaging, such as ultrasound and laparoscopy.[35][45][96][97]

Premature Ovarian Insufficiency

Premature ovarian insufficiency may arise from Turner syndrome, fragile X premutation, autoimmune conditions, or iatrogenic causes. This disorder typically manifests with amenorrhea, elevated FSH levels exceeding 25 mIU/mL, low AMH levels, and menopausal symptoms in women younger than 40. Differential diagnoses include other causes of anovulatory infertility, eg, luteal phase deficiency, hypothalamic amenorrhea, hyperprolactinemia, and Sheehan syndrome—pituitary necrosis resulting from postpartum hemorrhage that leads to hypogonadotropic hypogonadism characterized by low gonadotropin levels, absent ovulation, and amenorrhea, directly impairing fertility.[9][10][33][34][36][37]

Tubal and Uterine Factors

Tubal and uterine factors encompass tubal obstruction, most commonly secondary to PID or other inflammatory processes (eg, endometriosis), along with congenital or acquired uterine anomalies, which include a septate or bicornuate uterus, adenomyosis, leiomyomas, and Asherman syndrome (ie, intrauterine adhesions that interfere with implantation and embryo development).[32][96]

Male Factor Infertility

Male factor infertility may present with abnormal semen parameters (eg, low sperm count <15 million/mL, motility <40%), and contributes to 40% of infertility cases, often requiring concurrent evaluation to avoid misattributing infertility to female factors. Male factor infertility is usually associated with a normal female workup with abnormal semen analysis per WHO criteria.[98]

Unexplained Infertility

Unexplained infertility is diagnosed when no cause is identified after a complete workup, affecting 15% to 30% of cases.[15] Subclinical issues (eg, poor oocyte quality, immunological factors) may contribute but are not detectable with standard tests.[15][18]

Lifestyle or Environmental Factors

Lifestyle or environmental factors may not be a standalone diagnosis; obesity, smoking, excessive alcohol, and endocrine-disrupting chemicals (eg, phthalates) may exacerbate infertility across etiologies, affecting ovulation and implantation.[3][16][19]

Luteal Phase Defect

Luteal phase defect refers to inadequate progesterone production or an insufficient endometrial response during the luteal phase of the menstrual cycle, which can compromise embryo implantation and early pregnancy maintenance. Mid-luteal progesterone levels in this condition usually fall below 10 ng/mL, although some authorities propose a cutoff below 5 ng/mL.[33] The diagnosis remains controversial in female infertility due to limited agreement regarding its prevalence, diagnostic thresholds, and overall clinical relevance.[33][34]

Diagnosis requires identification of a luteal phase shorter than normal—typically under 10 to 12 days instead of the expected 14 days in a 28-day cycle—though ovulation assessment using basal body temperature provides unreliable results.[63] Luteal phase defect may result from disruptions in ovulation, hormonal regulation, endometrial receptivity, or from clomiphene use without concurrent progesterone supplementation, leading to an inadequate luteal phase.[10][34] Differentiation from anovulation is essential, as anovulatory cycles show mid-luteal progesterone levels below 3 ng/mL.[10][63]

Prognosis

Prognosis depends largely on age and the underlying cause of infertility. Women younger than 35 with ovulatory dysfunction achieve pregnancy in 70% to 80% of cases within 6 cycles.[63] IVF success declines with age, from a 47% to 50% live birth rate per transfer in women younger than 35 to approximately 10% in those older than 43.[99] Endometriosis and tubal factor infertility show spontaneous pregnancy rates of 10% to 20% without ART.[48] Unexplained infertility carries a 20% to 30% spontaneous pregnancy rate within 2 years.[80] Premature ovarian insufficiency has a spontaneous pregnancy rate below 5%, although outcomes improve with donor oocytes.[6]

A retrospective study comparing infertility treatments reported fecundability rates of 1.3% to 3.8% without treatment, 4% with IUI alone, 5.6% with clomiphene citrate alone, 8.3% with clomiphene plus IUI, 7.7% with gonadotropins alone, and 17.1% with gonadotropins combined with IUI.[94][100] Conversely, more recent data demonstrate the following age-related IVF outcomes: for women with infertility younger than 35, the live birth rate per cycle (LBR-pcyc) reaches 48.5%, with a live birth rate per embryo transfer (LBR-pet) of 51% for single embryo transfer and a cumulative LBR after 3 cycles (cLBR-3cyc) of 60% to 70%. For women with infertility ages 35 to 37, LBR-pcyc averages 38.3%, LBR-pet for single embryo transfer 40.3%, and cLBR-3cyc 54% to 61%. Women aged 38 to 40 achieve an LBR-pcyc of 26.8%, LBR-pet for single embryo transfer of 26.4%, and cLBR-3cyc of 40% to 50%. Those aged 41 to 42 experience LBR-pcyc rates of 11% to 13%, LBR-pet for single embryo transfer near 10%, and cLBR-3cyc between 21% and 25%. For women older than 42, LBR-pcyc declines to 4.1% to 7%, LBR-pet for single embryo transfer to 4% to 8%, and cLBR-3cyc falls below 10% without donor eggs.[3][14][92][93]

Complications

Ovarian Hyperstimulation Syndrome

OHSS occurs in about 1% to 6% of patients managed with IVF or ART, with 1% being severe cases with a higher risk of thrombosis.[101] OHSS results from an exaggerated response to the medications used to stimulate the ovaries to produce multiple eggs, engendered by the production of excessive hormones like vascular endothelial growth factor.[63] OHSS is characterized by enlarged ovaries and a range of symptoms caused

by fluid shifts in the body due to increased vascular permeability.[63] In mild cases, symptoms are usually self-limiting and primarily involve abdominal bloating, mild abdominal pain, nausea, and weight gain (up to 5-10 pounds).

Moderate cases may present with more pronounced bloating, moderate abdominal pain, vomiting, diarrhea, and ovarian enlargement (typically 8-12 cm in diameter). However, severe cases are associated with severe abdominal pain, significant weight gain (>10 pounds), ascites, pleural effusion, shortness of breath, reduced urine output, blood clots, electrolyte imbalances, and potential kidney or liver dysfunction, which may require intensive care management.[17][27][29][63][101] Cryopreservation, which involves rapid freezing and storage of embryos, may be a strategy to mitigate the risk of OHSS in the future management of patients with a high risk of developing OHSS.[46]

Pregnancy Complications

Multiple pregnancies happen in about 20% to 30% patients managed with ART, with increased preterm birth risk.[102] Ectopic pregnancy occurs in 2% to 5% with tubal factor infertility or IVF.[103] To reduce the risk of multiple pregnancy, the ASRM and the CDC recommend using elective single embryo transfer in ART, which reportedly drops the risk to less than 1%.[71][104]

Other Complications

The psychological impact associated with female infertility is also a significant challenge that clinicians must consider, with 40% of patients experiencing anxiety and 30% diagnosed with depression.[8] Surgical risks include bleeding (<1%) and infection (1%).[94] Long-term risks associated with female infertility include a slight ovarian cancer risk with an RR of 1.2.[14]

Deterrence and Patient Education

The deterrence of female infertility primarily involves the optimization of an individual's fertility and the mitigation of factors that can lead to the known pathophysiologic mechanisms underlying infertility. Lifestyle counseling, including smoking cessation, weight management to maintain a BMI of 19 to 25, and advising patients against excessive alcohol consumption or use of illicit drugs, can preserve fertility and reduce the incidence of female infertility.[11]

Screening for sexually transmitted infections and timely treatment if present, along with safe sexual practice, significantly reduces PID and its attendant complications, including female infertility.[53] Early evaluation and implementation of evidence-based effective management are recommended, especially in women older than 35, in whom failure of conception after 6 months, or in women younger than 35 but unable to get pregnant after 12 months, of unprotected sexual intercourse should prompt diagnosis and commencement of management of female infertility or timely referral.[33]

Women should be educated right from their youth about the age-related decline in fertility, with emphasis on the sharp decline after the age of 35, and should be given anticipatory counseling regarding options of oocyte harvesting and preservation if such patients elect not to become pregnant before the age of 35.[16] Participation in psychosocial support groups has been shown to reduce distress in 70% of patients.[8] Furthermore, the reality that even with IVF, some patients may not be able to achieve pregnancy that results in a live birth should be part of the initial discussions with the patients before committing resources to fertility treatment.[71] Additionally, such discussions should include alternative options to IVF, eg, adoption and surrogate conception (gestational surrogacy or nongestational surrogacy).[102]

Enhancing Healthcare Team Outcomes

IVF and related ART provide advanced options for treating infertility, particularly when conservative or pharmacologic interventions fail. IVF protocols, including antagonist and long agonist regimens, optimize follicular stimulation, prevent premature LH surge, and enhance oocyte retrieval outcomes. Success depends on patient age, ovarian reserve, embryo quality, and lifestyle factors, with cumulative live birth rates reaching up to 70% in younger women. Adjunct procedures such as preimplantation genetic testing, frozen embryo transfer, and individualized luteal support further improve outcomes while minimizing risks such as ovarian hyperstimulation syndrome.

Effective infertility management requires coordinated interprofessional collaboration among physicians, general practitioners, advanced practitioners, nurses, pharmacists, and laboratory specialists. Physicians and advanced practitioners design and monitor treatment protocols, while nurses provide education, counseling, and cycle tracking support. Pharmacists ensure correct dosing and safe hormone administration. Ongoing communication across the team fosters patient-centered decision-making, enhances adherence, reduces complications, and improves reproductive outcomes.

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