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Infertility: causes, diagnostic approaches, and treatment modalities-An updated review

Sahar Adi Albogamy
KSA, National Guard Health Affairs

Ahmad Alhelo Alanazi
KSA, National Guard Health Affairs

Mona Mudlah Alsaadi
KSA, National Guard Health Affairs

Ruqiah Ali Alzaher
KSA, National Guard Health Affairs

Hussain Mahdi Aljawad
KSA, National Guard Health Affairs

Ali Suliman Al Aloula
KSA, National Guard Health Affairs

Barakat Shumailan Alazmiy
KSA, National Guard Health Affairs

Majed Khalid Aljarallah
KSA, National Guard Health Affairs

Yussef Falah Alharbi
KSA, National Guard Health Affairs

Khalid Assaf Almutairi
KSA, National Guard Health Affairs

Mohammed Rashed Al Otaibi
KSA, National Guard Health Affairs

Mohammad Aljehani
KSA, National Guard Health Affairs

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***Corresponding email**: akk29337@gmail.com*
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Hamdi Saleem Alharbi
KSA, National Guard Health Affairs

Mohammed Saad Ali Al-Harbi
KSA, National Guard Health Affairs

Fouad Hamed Alamri
KSA, National Guard Health Affairs

***Abstract*---Background:** Infertility significantly affects individuals' psychological and physical well-being, with notable implications for couples. This review primarily focuses on female infertility, emphasizing the importance of understanding normal fecundability and its impact on clinical management. **Aim:** To provide an updated review of the causes, diagnostic approaches, and treatment modalities for female infertility. **Methods:** A comprehensive literature review was conducted to analyze the prevalence, etiological factors, pathophysiology, diagnostic strategies, and treatment options for female infertility. **Results:** Findings indicate that ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (12%), and tubal abnormalities (11%) are common causes of female infertility. The prevalence of infertility rises significantly with age, with 30% of women aged 40-44 experiencing infertility. Diagnostic evaluations involve detailed medical history, physical examinations, and various imaging and hormonal tests. **Conclusion:** Understanding the multifaceted nature of female infertility is crucial for effective diagnosis and management. While the review highlights significant factors contributing to infertility, it also underscores the necessity for integrated care approaches that involve both partners. Future research should focus on advancements in treatment modalities and addressing psychosocial aspects to enhance overall well-being.

***Keywords*---**infertility, female, fecundability, diagnostic approaches, treatment modalities.

Introduction

Infertility represents a medical condition that has wide-ranging impacts on psychological, physical, mental, spiritual, and medical well-being. A distinguishing aspect of infertility is its dual effect on both the individual and their partner, influencing them as a couple. While male infertility is an integral part of the broader infertility discourse, this particular discussion focuses on the evaluation, management, and treatment of female infertility. Understanding infertility requires knowledge of normal fecundability, which refers to the likelihood of achieving pregnancy within a single menstrual cycle. This foundational knowledge enables healthcare providers to appropriately counsel patients on potential referrals and deliver essential education regarding the

condition. Extensive research has been conducted to establish fecundability rates, which have subsequently contributed to the determination of normal pregnancy rates, facilitating the diagnosis of infertility. The largest of these studies revealed that approximately 85% of women conceive within 12 months. According to this study, fecundability is 25% during the first three months of unprotected intercourse, after which it declines to 15% over the following nine months [1]. These findings have informed the American Society of Reproductive Medicine (ASRM) in setting guidelines for when couples should be evaluated for infertility. The ASRM recommends beginning infertility assessments after 12 months of unsuccessful attempts to conceive through unprotected intercourse or therapeutic donor insemination in women under 35, and after 6 months for women over 35 [2].

Etiology

The World Health Organization (WHO) conducted a comprehensive multinational study to investigate gender distribution and the causes of infertility. The study revealed that female infertility accounted for 37% of cases, while in 35% of couples, both male and female factors contributed to infertility. Male factor infertility was identified in 8% of cases [3]. Among the most common identifiable causes of female infertility reported in this study were:

- Ovulatory disorders: 25%
- Endometriosis: 15%
- Pelvic adhesions: 12%
- Tubal blockage: 11%
- Other tubal/uterine abnormalities: 11%
- Hyperprolactinemia: 7%

These etiological factors are explored in greater detail later, while male infertility and unknown factors fall outside the scope of this discussion. Nonetheless, it is essential to acknowledge that male factor infertility accounts for a significant portion of infertility cases.

Epidemiology

According to a study from the National Survey of Family Growth, which involved interviews with 12,000 women in the United States, infertility prevalence declines with increasing age. As women age, the likelihood of experiencing infertility rises. Among women aged 15 to 34, infertility rates ranged from 7.3% to 9.1%. This percentage rose to 25% in women aged 35 to 39, and in women aged 40 to 44, the infertility rate reached 30% [4]. Globally, infertility rates are higher in regions such as Eastern Europe, North Africa, and the Middle East. Around 2% of women aged 20 to 44 globally were unable to achieve a live birth, and 11% of women with prior live births were unable to conceive again [5].

Pathophysiology
Anovulation:

Ovulatory dysfunction accounts for approximately 25% of identified causes of female infertility. Oligo-ovulation or anovulation results in infertility due to the

absence of monthly oocyte release, preventing fertilization and subsequent pregnancy. To aid in classification and treatment, the World Health Organization (WHO) has categorized ovulatory disorders into four distinct types:

- Hypogonadotropic hypogonadal anovulation: Hypothalamic amenorrhea
- Normogonadotropic normoestrogenic anovulation: Polycystic ovarian syndrome (PCOS)
- Hypergonadotropic hypoestrogenic anovulation: Premature ovarian failure
- Hyperprolactinemic anovulation: Pituitary adenoma

Hypothalamic amenorrhea, also referred to as functional hypothalamic amenorrhea (FHA), is associated with excessive exercise or eating disorders, both of which lower hypothalamic GnRH secretion [6]. Caloric restriction, weight loss, or intense exercise elevate cortisol levels, inhibiting GnRH secretion [7]. This impaired GnRH pulsatility diminishes the release of gonadotropins, specifically follicle-stimulating hormone (FSH) and luteinizing hormone (LH), from the anterior pituitary, which, in turn, affects follicular growth, results in anovulation, and reduces estrogen levels [8]. Although FSH and LH levels can vary between normal and low, their ratio reflects that of a prepubertal female, with higher FSH than LH [8]. The most frequent form of **normogonadotropic normoestrogenic anovulation** is PCOS, which contributes to 80%-85% of all cases of anovulation and impacts roughly 8% of women of reproductive age [9]. PCOS diagnosis is based on the Rotterdam criteria, which requires at least two out of the following three conditions, excluding other potential causes:

- Oligoovulation/anovulation
- Clinical or biochemical signs of hyperandrogenism
- Polycystic ovaries visible on ultrasound [10]

Infertility associated with PCOS is likely related to impaired follicular maturation, which leads to anovulation, though FSH and estrogen typically remain within normal limits, and LH may be normal or elevated. The pathophysiology of PCOS-related infertility is not fully understood, but abnormal GnRH pulsatility is often considered a possible explanation. The elevated anti-Mullerian hormone (AMH) correlates with the high number of arrested follicles and polycystic ovaries [11].

Hypergonadotropic hypoestrogenic anovulation, which includes premature ovarian insufficiency (POI) and ovarian resistance, is often linked to a woman's age. As previously mentioned, advancing age reduces fertility due to the well-documented decline in oocyte quality and quantity. By 20 weeks of gestation, a female fetus has around 6 million follicles, which drops to 1 million at birth and to 300,000 by puberty [12]. This follicular depletion accelerates in the mid-30s [13]. External factors, particularly cigarette smoking, exacerbate the reduction in follicle quantity. Smoking has been shown to inversely affect fecundability and follicle count, leading to early menopause (before age 40), with smokers experiencing a 30% higher risk [14].

Oocyte quality also diminishes with age, with meiotic nondisjunction events increasing, leading to aneuploidy. This phenomenon is believed to result from accumulated cellular damage and age-related alterations in granulosa cells [15]. As women age, the prevalence of chromosomal abnormalities in oocytes and embryos rises significantly [15]. Primary ovarian insufficiency (POI), characterized

by hypergonadotropic hypogonadism before age 40, results in a lack of folliculogenesis, reduced estrogen production, oocyte loss, and infertility [16]. The most common cause of POI is Turner syndrome, which involves a monosomy of the sex chromosomes, producing a 45X karyotype [17]. A detailed discussion of Turner syndrome falls outside the scope of this manuscript.

As noted earlier, WHO recognizes **hyperprolactinemia** as a significant cause of female infertility; however, recent guidelines from the American Society for Reproductive Medicine (ASRM) suggest that prolactin evaluation is not mandatory in the initial infertility workup [2]. Elevated prolactin levels suppress hypothalamic GnRH secretion, which reduces LH secretion and results in anovulation, along with oligomenorrhea or amenorrhea. Prolactin levels between 20 and 50 ng/mL interfere with progesterone release, shortening the luteal phase. While still debated, hyperprolactinemia may contribute to luteal phase defects and infertility. Prolactin concentrations between 50 and 100 ng/mL cause oligomenorrhea or amenorrhea, while values over 100 ng/mL are associated with overt hypogonadism and pituitary adenomas [18].

Endometriosis

Endometriosis is defined by the presence of endometrial tissue outside the uterine cavity, diagnosed through histological confirmation of endometrial glands or stroma outside the uterus. While it most commonly affects the pelvis, it may spread throughout the abdominal cavity and impacts 10%-15% of women of reproductive age [19]. Between 40%-50% of women with endometriosis experience infertility [20]. Endometriosis is classified into four stages according to the American Society of Reproductive Medicine, with stage I being minimal and stage IV severe. The pathophysiology of infertility differs depending on the stage. In stages I and II, inflammation, elevated prostaglandins, cytokines, macrophages, and natural killer cells disrupt ovarian and tubal function, impairing follicle formation, fertilization, and implantation [22][23]. In stages III and IV, pelvic adhesions and masses distort the pelvic anatomy, hindering tubal and oocyte mobility and sperm transport [24]. Advanced endometriosis may also affect folliculogenesis, lowering the chances of fertilization [25].

Pelvic/Tubal Adhesions

Pelvic and tubal adhesions, along with uterine and tubal abnormalities, account for a significant portion of female infertility. Infectious processes within the abdomen, particularly pelvic inflammatory disease (PID), are the primary cause of pelvic and tubal adhesions. Chlamydia trachomatis is the microorganism most strongly associated with PID-induced infertility, with one in four women with tubal infertility testing positive for Chlamydia antibodies, which inversely correlates with pregnancy rates [26]. Infertility likelihood increases with the number of PID episodes and their severity. One study found pregnancy rates of 89% after one episode, 77% after two, and 46% after three [27]. For mild, moderate, and severe PID, live birth rates were 90%, 82%, and 57%, respectively [28]. Hydrosalpinx, a condition caused by chronic tubal inflammation, leads to tubal obstruction and fluid accumulation in the fallopian tubes. Hydrosalpinx impairs fertility by allowing retrograde flow of toxins and prostaglandins into the

endometrium, which hinders implantation by disrupting endometrial receptivity [29]. In vitro fertilization (IVF) outcomes are reduced by 50% in the presence of a hydrosalpinx [30].

Uterine Factors

Infertility stemming from uterine factors is linked either to space-occupying lesions or diminished endometrial receptivity. In the case of uterine leiomyomas (fibroids), a meta-analysis indicated that only submucosal or intracavitary fibroids hindered implantation and reduced pregnancy rates when compared to other infertile controls [31]. Congenital uterine abnormalities (CUA), though uncommon, are also linked to infertility, with uterine septums being the most prevalent, and frequently associated with recurrent pregnancy loss. Interestingly, one study found that the occurrence of CUAs is identical in both fertile and infertile populations [32]. CUAs are believed to account for around 8% of female infertility causes; however, approximately 25% of women who experience late first-trimester or second-trimester miscarriages are diagnosed with CUAs [33]. A comprehensive analysis of CUA classifications and pathophysiology falls beyond the scope of this manuscript.

History and Physical Examination

The evaluation for infertility is recommended for women who have been unsuccessful in conceiving after 12 months of unprotected intercourse, or 6 months if they are over 35 years old [34]. While this discussion focuses on female infertility, it is crucial to remember that a simultaneous evaluation of male infertility is necessary. In cases where donor sperm is being considered, women should undergo the standard female infertility assessment before insemination [2]. Key components of the infertile woman’s medical history include the following:

- Duration of infertility
- Obstetric history
- Menstrual history, including molimina
- Medical, surgical, and gynecological history, with emphasis on sexually transmitted infections
- Sexual history, encompassing coital frequency and timing
- Male partner's history, including any issues with erection or ejaculation
- Social and lifestyle history, covering smoking, alcohol, illicit drug use, exercise, diet, and occupation
- Family history, screening for genetic disorders, venous thrombotic events, recurrent pregnancy loss, and infertility

A thorough physical examination should cover:

- Vital signs and body mass index
- Thyroid assessment
- Breast examination for galactorrhea
- Indicators of androgen excess: dermatological and genital examination
- Abnormalities in vaginal or cervical anatomy
- Detection of pelvic masses or tenderness
- Uterine enlargement or irregularity

- Transvaginal ultrasonography at the bedside as part of the initial physical assessment

Evaluation

The diagnostic process for infertility is categorized into five main areas:

1. Semen analysis
2. Evaluation of ovarian function and reserve
3. Assessment of the uterine cavity
4. Examination of the fallopian tubes
5. Endocrinological serum studies

Although semen analysis interpretation is beyond the scope of this review, it is critical to emphasize its importance in the initial evaluation prior to any treatment.

Ovarian function can often be assessed based on menstrual cycle history. Women with regular, predictable cycles and typical symptoms such as molimina (e.g., bloating, fatigue, breast tenderness) are likely ovulating. At-home urinary LH predictor kits detect mid-cycle LH surges, indirectly confirming ovulation and aiding in identifying the fertile window [35]. Ovulation can also be confirmed through a day-21 progesterone serum test or a mid-luteal phase progesterone test, ideally performed approximately one week before menstruation. A progesterone level above 3 ng/mL indicates ovulation [36]. A more invasive but accurate method to confirm ovulation involves daily ultrasounds to monitor follicle development and disappearance [37].

Several tests exist to assess ovarian reserve, with the two most commonly used being the Cycle Day 3 FSH and estradiol levels, and the Anti-Mullerian Hormone (AMH) test. Cycle Day 3 FSH and estradiol testing measures ovarian reserve by observing the hormones produced by small follicles; lower FSH levels indicate better ovarian reserve. Studies show that FSH levels below 10 IU/mL are associated with a normal ovarian reserve, levels between 10 and 20 IU/mL indicate intermediate reserve, and levels above 20 IU/mL suggest poor ovarian reserve, with diminished chances of spontaneous ovulation [38]. Estradiol levels below 80 pg/mL on Day 3 indicate adequate ovarian reserve, while levels exceeding 80 pg/mL correlate with reduced pregnancy rates; values above 100 pg/mL are associated with a 0% pregnancy rate [39].

AMH, produced by preantral and antral follicles, serves as a marker of ovarian function that can be measured at any point in a woman's menstrual cycle [40]. AMH levels decrease steadily throughout a woman's reproductive life until becoming undetectable at menopause [41]. AMH is also a valuable predictor of response to exogenous gonadotropins [42]:

- Less than 0.5 ng/mL: Indicates difficulty in growing more than three follicles
- Less than 1.0 ng/mL: Suggests limited egg supply requiring aggressive ovulation induction protocols
- 1.0 to 3.5 ng/mL: Reflects normal ovarian reserve

- Greater than 3.5 ng/mL: Indicates a sufficient egg supply, where mild induction may prevent ovarian hyperstimulation syndrome

It is important to note that while ovarian reserve tests are reliable for predicting ovulation induction outcomes, they are not diagnostic for live birth rates. These tests should not be used to exclude patients from in vitro fertilization (IVF) treatment [43]. Additionally, antral follicle counts, conducted via transvaginal ultrasound in the early follicular phase, offer an accurate measure of ovarian reserve and can predict ovarian response to stimulation [44].

Tubal Assessment

The definitive method for evaluating tubal patency is laparoscopy combined with chromopertubation. This procedure is recommended as a primary diagnostic tool for suspected pelvic adhesions, endometriosis, or other pelvic disorders. However, due to its high specificity and lower invasiveness, the hysterosalpingogram (HSG) is more frequently employed as the initial assessment for tubal patency and abnormalities [45]. The HSG is particularly effective in detecting proximal occlusions, followed by distal occlusions, although it has limited predictive value for intrauterine and tubal adhesions [46]. Additionally, using oil-soluble media in HSG has been associated with improved pregnancy and live birth rates. A meta-analysis indicated that after undergoing HSG, the rates of pregnancy and live births significantly increased compared to control groups (overall response, 2.98; 95% CI 1.05-6.37) [47].

Uterine Cavity Assessment

The gold standard for evaluating the uterine cavity is hysteroscopy, which enables direct visualization of intrauterine pathologies and allows for immediate surgical intervention if needed. Despite hysteroscopy being considered the gold standard, a less invasive technique, the saline infusion sonogram (SIS), is more commonly used. The SIS demonstrates high sensitivity and specificity for identifying all intrauterine abnormalities and serves as an effective screening tool prior to infertility treatment, whether or not three-dimensional modeling is employed [48]

Treatment and Management
Lifestyle Changes

Infertility and ovulatory dysfunction are often linked to extremes in body mass index (BMI). Women with a BMI below 17 kg/m², especially those engaging in intense exercise or suffering from eating disorders, may experience hypogonadotropic hypogonadism due to diminished pituitary gonadotropin secretion [49]. In the United States, controlled ovarian stimulation with exogenous gonadotropins is commonly used to induce ovulation. In contrast, European protocols may include pulsatile GnRH therapy for women unresponsive to initial treatments [51]. A study highlighted the significance of behavioral modifications in restoring ovulation, with 87% of women achieving regular ovarian function after receiving individualized therapy to address energy deficiencies and behavioral issues [52]. Conversely, women with a BMI exceeding 27 kg/m² can enhance ovulation through weight loss alone. Research indicates that losing 10%

of body weight can restore normal ovulation in 50% to 100% of these women within a year [53]. However, a study revealed that while counseling and interventions for weight loss before infertility treatment are beneficial, they do not significantly improve pregnancy or live birth rates compared to obese women undergoing infertility treatment without weight-loss measures. Thus, there is no specific BMI requirement to initiate fertility treatment [54].

Controlled Ovarian Hyperstimulation

The first-line medication for unexplained infertility is clomiphene citrate (CC), a selective estrogen receptor modulator (SERM) that enhances gonadotropin release from the anterior pituitary. Clomiphene is effective for WHO class 2 anovulation but ineffective for WHO class 1 and class 3 anovulation. Treatment typically starts with a dosage of 50 mg on cycle days 2, 3, 4, or 5 for five consecutive days, with couples advised to engage in intercourse every other day for one week, beginning five days after completing the medication. The chances of pregnancy increase when clomiphene is combined with intrauterine insemination (IUI). The initiation day of the medication (cycle days 2 to 5) does not significantly affect ovulation, pregnancy, or live birth rates [55].

Letrozole, an aromatase inhibitor that suppresses estrogen production by inhibiting the conversion of androstenedione and testosterone to estrone and estradiol, is another widely used oral medication for ovulation induction. Although letrozole is FDA-approved for breast cancer adjuvant therapy, its use for inducing ovulation is considered off-label. However, extensive literature supports its efficacy and safety in this context. Letrozole is administered starting at doses of 2.5, 5, or 7.5 mg/day on cycle days 3, 4, 5, 6, and 7, with intercourse scheduled every other day five days after completing the medication. The American College of Obstetricians and Gynecologists (ACOG) recommends letrozole as the first-line treatment for women with polycystic ovary syndrome (PCOS) over clomiphene due to several advantages:

- Higher rate of monofollicular development and reduced incidence of twin pregnancies.
- Shorter half-life.
- No antiestrogenic effects on the endometrium or central nervous system.
- Lower estradiol levels, beneficial for women with breast cancer undergoing in vitro fertilization (IVF).

Given these benefits, letrozole may increasingly replace clomiphene as the first-line treatment for ovulation induction [57][58].

Gonadotropin therapy is a more intensive regimen used for WHO class 1, 2, or 3 anovulatory disorders and serves as a second-line option for women who do not conceive after multiple cycles of clomiphene. Studies indicate a higher live birth rate with gonadotropins compared to ongoing clomiphene treatment [59]. Various dosing protocols are utilized depending on provider preferences and the chosen infertility treatment, which are beyond the scope of this review. However, it is crucial to monitor patients closely when using gonadotropins. Transvaginal ultrasounds are employed every 2 to 3 days during the late follicular phase to assess follicular growth. A mature follicle is defined as being over 18 mm in diameter with estradiol levels exceeding 200 pg/mL. Once a mature follicle is

identified, an injection of 250 mg recombinant hCG subcutaneously or 10,000 U of urinary-derived hCG intramuscularly is administered to trigger ovulation [60]. Following this trigger, IUI is performed 24 to 36 hours later. IUI can be combined with any ovarian induction agent, and its use alongside medications is encouraged to enhance pregnancy rates. The superiority of allowing a natural LH surge versus administering an hCG trigger before IUI remains unclear. A meta-analysis conducted in 2010 found no definitive advantage of one method over the other, suggesting that the choice should be based on factors such as cost, staffing limitations, and patient convenience [61].

Treatment / Management
Lifestyle Changes

Women with extreme body mass index (BMI) often experience infertility and ovulatory dysfunction. Specifically, those with a BMI below 17 kg/m^2—particularly if they have a history of intense exercise or eating disorders—may develop hypogonadotropic hypogonadism, resulting in reduced secretion of pituitary gonadotropins. In the U.S., controlled ovarian stimulation with exogenous gonadotropins is typically used to induce ovulation, whereas women in Europe who do not respond to this therapy may receive pulsatile GnRH therapy. Notably, a study indicated that behavioral changes aimed at correcting energy deficiencies could restore normal ovarian function in 87% of affected women, improving their BMI.

Conversely, women with a BMI over 27 kg/m^2 can often achieve ovulation through weight loss alone, with research showing that losing 10% of body weight can restore normal ovulation rates in 50% to 100% of cases within a year. However, a study found that counseling for weight loss prior to infertility treatment did not yield higher pregnancy or live birth rates when compared to obese women receiving infertility treatments without weight-loss interventions. Thus, a specific BMI requirement is not necessary for initiating fertility treatment.

Controlled Ovarian Hyperstimulation

Clomiphene citrate (CC) is the first-line medication for treating infertility of unknown origin and is frequently utilized by healthcare providers. As a selective estrogen receptor modulator (SERM), clomiphene increases gonadotropin release from the anterior pituitary. It is effective for WHO class 2 anovulation but not for classes 1 and 3. The standard dosing begins at 50 mg on cycle days 2, 3, 4, or 5 for five consecutive days, with intercourse recommended every other day starting five days after the last pill. Combining clomiphene with intrauterine insemination (IUI) may further increase pregnancy odds. Research indicates that the initiation day of medication (between cycle days 2 to 5) does not significantly affect ovulation, pregnancy, or live birth rates.

Letrozole, an aromatase inhibitor, is another commonly used oral medication for ovulation induction. While it is FDA-approved for breast cancer treatment, its off-label use for ovulation induction is supported by extensive literature. Letrozole is typically administered at doses of 2.5, 5, or 7.5 mg daily on cycle days 3 to 7, with intercourse advised five days after completing the medication, mirroring the

approach with clomiphene. The American College of Obstetricians and Gynecologists (ACOG) recommends letrozole as the first-line treatment for women with polycystic ovary syndrome (PCOS) over clomiphene due to its favorable profile, which includes a higher rate of monofollicular development, a lower risk of twin pregnancies, no adverse antiestrogenic effects, and lower estradiol levels.

Gonadotropin therapy serves as a more intensive regimen for WHO Class 1, 2, or 3 anovulatory disorders. This second-line option is indicated for women who have not conceived after several cycles of clomiphene. Some studies suggest improved live birth rates with gonadotropins compared to ongoing clomiphene treatment. Treatment protocols vary, requiring close monitoring through transvaginal ultrasounds to evaluate follicular growth, with a mature follicle defined as being over 18 mm in diameter and estradiol levels above 200 pg/mL. Following identification of a mature follicle, a trigger injection of either 250 mg recombinant HCG or 10,000 U of urinary-derived HCG is administered to induce ovulation, typically followed by IUI 24-36 hours later. While there is some uncertainty regarding the benefits of a natural LH surge versus an HCG trigger before IUI, treatment decisions should consider cost, staffing, and patient convenience.

Tubal and Pelvic Adhesions

In vitro fertilization (IVF) is the primary treatment for bilateral tubal factor infertility, as tubal corrective surgeries often yield poorer pregnancy outcomes and a higher risk of ectopic pregnancies. Women with severe tubal conditions, such as hydrosalpinx, are advised to undergo bilateral salpingectomy to enhance IVF pregnancy rates. For those with mild distal tubal disease, fimbrioplasty can enable multiple pregnancies without IVF. Although one study found comparable pregnancy rates between mild tubal disease and IVF, the ectopic pregnancy risk was significantly higher with the former. Women with prior bilateral salpingectomy or tubal ligation for contraception constitute an essential population for tubal factors. Healthcare providers must discuss the potential for regret with women considering tubal ligation. Pregnancy chances post-tubal reanastomosis depend on age, ligation type, and available tubal length, with younger women who had a ring or clip ligation and over 4 cm of remaining tube being ideal candidates, achieving pregnancy rates similar to IVF. However, time to pregnancy after tubal surgery tends to be longer than with IVF.

Uterine Abnormalities

The impact of leiomyomas on infertility and live birth rates remains uncertain, though a complete infertility evaluation is recommended before investigating fibroids further. The critical factor regarding fibroids is their location; those that distort the uterine cavity can impair implantation and raise miscarriage risks. Women with submucosal or submucosal-intramural fibroids that distort the cavity experience decreased pregnancy rates, but removal of these fibroids can improve outcomes. Operative hysteroscopy is the first-line treatment for excising these detrimental fibroids. Other uterine issues, like synechiae and septa, may lead to recurrent pregnancy loss but can also contribute to infertility. Successful operative hysteroscopy has been shown to significantly reduce pregnancy loss in patients with these conditions. Additionally, asymptomatic polyps can hinder

fertility; one study revealed that polypectomy in asymptomatic infertile women prior to IUI raised pregnancy rates from 28% to 63%.

IVF Procedures

This section offers an overview of IVF procedures while excluding medication protocols. Controlled ovarian hyperstimulation typically employs injectable gonadotropins. Approximately 36 hours after an HCG trigger shot, a specialist performs transvaginal ultrasound-guided oocyte retrieval. Following retrieval, oocytes are placed in a specialized medium, and normal sperm are introduced for insemination. If sperm abnormalities exist, intracytoplasmic sperm injection (ICSI) is utilized, whereby a single sperm is injected directly into the egg cytoplasm. Post-fertilization, embryos are assessed and graded, with subsequent transfer occurring on either Day 3 or Day 5. Preimplantation genetic testing (PGT) is an additional IVF procedure aimed at detecting known parental genetic mutations, balanced translocations, or chromosomal abnormalities such as aneuploidy. PGT is particularly advantageous for couples with known genetic issues, advanced maternal age, repeated IVF failures, recurrent pregnancy loss, or unexplained infertility.

Differential Diagnosis

Infertility is a multifaceted disorder significantly impacting couples. It is crucial to recognize that multiple infertility causes may exist concurrently, necessitating a comprehensive workup to exclude harmful diseases. Given the high prevalence of polycystic ovary syndrome (PCOS) within the infertile demographic, this discussion focuses on its differential diagnosis, which includes:

- Androgen-producing ovarian tumors
- Adrenal tumors
- Nonclassic congenital adrenal hyperplasia
- Cushing syndrome
- Prolactinemia disorders
- Thyroid disorders

Evaluating PCOS should involve measuring total testosterone, DHEA-S, and 17-Hydroxyprogesterone to investigate potential virilizing ovarian or adrenal tumors or nonclassic congenital adrenal hyperplasia. While it's advised that DHEA-S testing is reserved for women with pronounced virilization, an asymptomatic elevation does not typically alter management strategies. Additionally, levels of prolactin and thyroid-stimulating hormones should be assessed.

- The upper limit of normal for female testosterone is 45 to 60 ng/dL.
- A testosterone value exceeding 150 ng/dL necessitates investigation for ovarian and adrenal androgen-secreting tumors.
- DHEA-S levels above 500 to 700 mcg/dL require further evaluation for adrenal tumors.
- Fasting 17-hydroxyprogesterone levels over 200 ng/dL collected during the follicular phase call for an ACTH stimulation test, with levels exceeding 500 ng/dL being diagnostic for nonclassic congenital adrenal hyperplasia.

The clinical signs and further evaluation of these disorders are beyond the scope of this paper.

Prognosis

This section summarizes pregnancy rates per treatment cycle across various modalities, primarily from studies evaluating unexplained infertility but applicable to other known causes. Pregnancy rates vary significantly based on individual factors:

- No treatment: 1.3% to 3.8%
- IUI alone: 4%
- Clomiphene citrate (CC) alone: 5.6%
- CC with IUI: 8.3%
- Gonadotropins alone: 7.7%
- Gonadotropins with IUI: 17.1%
- IVF: 20.7%

Letrozole alone and letrozole with IUI yield similar pregnancy rates to CC with IUI, serving as options for women for whom IVF is not feasible and who have not succeeded with CC plus IUI. A 2009 study indicated that women failing CC plus IUI should transition directly to IVF rather than undergoing gonadotropins plus IUI first. This approach resulted in a shorter time to pregnancy, fewer treatment cycles, and lower total costs per delivery. Although IVF pregnancy rates have since improved, evidence still indicates that IVF offers the highest pregnancy rates among treatment options. The research indicates that clomiphene can be utilized as a first-line treatment for infertility, although this perspective has evolved. A 2008 systematic review suggested that clomiphene may not significantly enhance ovulation rates compared to no treatment. While it remains a prominent therapy, women who do not conceive after three cycles should consider alternative treatments like letrozole or direct IVF. Women over 40 with diminished ovarian reserve should also proceed with IVF if they have not conceived after three cycles of clomiphene or letrozole.

Complications:

The primary complications associated with infertility treatments include multiple gestations, ectopic pregnancies, and ovarian hyperstimulation syndrome (OHSS).

Multiple Gestations

The risk of multiple gestations has been a persistent concern within artificial reproductive technologies (ART) since their inception. In the United States, approximately 32% of pregnancies resulting from assisted reproductive technologies are multiple births, compared to only 3.4% of naturally conceived pregnancies . According to the Centers for Disease Control and Prevention (CDC), in 2009, the probabilities of singleton, twin, and higher-order pregnancies resulting from in vitro fertilization (IVF) with fresh embryo transfer were 62%, 29%, and 3%, respectively . Oral ovulation induction agents such as clomiphene and letrozole present a lower risk of multiple gestations compared to gonadotropins, with observed rates of twins, triplets, and quadruplets at 7%,

0.5%, and 0.3%, respectively. In contrast, gonadotropins have been associated with a 13% likelihood of multiple gestations, including triplets . Currently, the American Society for Reproductive Medicine (ASRM) and the CDC advocate for the implementation of elective single embryo transfer (eSET) for patients with a favorable prognosis. The adoption of eSET has led to a decrease in the rates of twins and triplets to less than 1%. Furthermore, there is ongoing debate regarding the appropriateness of using gonadotropins for ovulation induction outside of IVF protocols, given the elevated risk of multiple gestations . As IVF utilization continues to rise, the employment of gonadotropins in conjunction with intrauterine insemination (IUI) is likely to diminish.

Ectopic Pregnancy:

Ectopic pregnancy represents another significant risk following infertility treatments, necessitating thorough counseling for patients. The incidence of ectopic pregnancies among infertility patients is approximately two to three times higher than that of the general population, often linked to a substantial proportion of tubal factor infertility . The highest risk for ectopic pregnancy is associated with surgical interventions aimed at correcting tubal factor infertility, with rates reported as high as 30% following tubal reconstructive surgery . In the context of IVF fresh embryo transfers, the risk of ectopic pregnancy is greater than that of frozen embryo transfers, with an overall incidence of around 1.3% . Notably, the use of ovulation induction agents combined with IUI does not appear to increase the risk of ectopic pregnancies compared to natural conception; however, a large-scale study indicated ectopic pregnancy rates of 4%, 6%, and 8% for clomiphene, letrozole, and gonadotropins, respectively .

Ovarian Hyperstimulation Syndrome:

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication resulting from controlled ovarian hyperstimulation. OHSS can manifest with a diverse array of signs and symptoms, ranging from abdominal distension, nausea, and vomiting to more severe complications such as renal failure, venous thrombosis, acute respiratory distress syndrome, electrolyte imbalances, cardiac arrhythmias, and sepsis. If left untreated, severe cases of OHSS can lead to mortality due to these complications. Golan et al. classified the various stages of OHSS in 1989 . The underlying pathophysiological mechanism involves increased capillary permeability, leading to fluid shifts into the third space. Women exhibiting greater than 20 mature follicles who also receive a human chorionic gonadotropin (HCG) trigger shot are at the highest risk of developing OHSS. The incidence of moderate and severe OHSS following IVF is estimated to be between 6% and 1%, respectively .

Conclusion

Infertility remains a pressing global health issue, with profound implications for affected individuals and couples. This updated review provides a comprehensive overview of female infertility, emphasizing its complex etiology and the necessity for thorough diagnostic evaluations. The prevalence of infertility varies significantly with age, highlighting the critical role of reproductive aging in female

fecundability. As women age, the likelihood of experiencing infertility increases substantially, which calls for early intervention strategies and appropriate counseling. The etiological factors contributing to female infertility are diverse, with ovulatory disorders being the most prevalent. Conditions such as polycystic ovary syndrome (PCOS), endometriosis, and pelvic adhesions necessitate multifaceted approaches to diagnosis and management. The incorporation of detailed medical histories and targeted physical examinations is vital for identifying underlying causes. Moreover, advancements in diagnostic technologies and treatment modalities have expanded the options available for women struggling with infertility. While traditional treatment modalities, including ovulation induction and assisted reproductive technologies, remain central to managing infertility, a holistic approach that considers psychological and social dimensions is crucial. Psychological counseling can enhance emotional resilience and improve treatment outcomes for couples facing infertility challenges. Furthermore, collaborative care models involving both partners are essential for effective management, as infertility impacts not only the woman but also her partner. In conclusion, addressing female infertility requires a multifaceted approach that encompasses a comprehensive understanding of its causes, diagnostic procedures, and treatment options. Continued research and innovation in reproductive health are imperative to optimize care and support for individuals and couples experiencing infertility. Future studies should also explore the intersection of medical and psychosocial factors, further enhancing the quality of care provided to this population.

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الملخص:

الخلفية :يؤثر العقم بشكل كبير على الصحة النفسية والبدنية للأفراد، مع تداعيات ملحوظة على الأزواج. تركز هذه المراجعة بشكل أساسي على العقم لدى النساء، مع التأكيد على أهمية فهم القدرة الطبيعية على الإنجاب وتأثيرها على الإدارة السريرية.

الهدف :تقديم مراجعة محدثة للأسباب، طرق التشخيص، وأساليب العلاج للعقم لدى النساء.

الطرق :تم إجراء مراجعة شاملة للأدبيات لتحليل انتشار العقم، والعوامل المسببة، والفيزيولوجيا المرضية، واستراتيجيات التشخيص، وخيارات العلاج للعقم لدى النساء.

النتائج :تشير النتائج إلى أن الاضطرابات الإباضية (25%)، وانتباذ بطانة الرحم (15%)، والتصاقات الحوض (12%)، والعيوب الأنبوبية (11%) هي من الأسباب الشائعة للعقم لدى النساء. يرتفع انتشار العقم بشكل كبير مع تقدم العمر، حيث تعاني 30% من النساء اللاتي تتراوح أعمارهن بين 40-44 عامًا من العقم. تشمل التقييمات التشخيصية التاريخ الطبي التفصيلي، الفحوصات البدنية، والاختبارات التصويرية والهرمونية المتنوعة.

الاستنتاج :فهم الطبيعة متعددة الأبعاد للعقم لدى النساء أمر حيوي للتشخيص الفعال والإدارة. بينما تسلط المراجعة الضوء على العوامل المهمة التي تسهم في العقم، فإنها تؤكد أيضًا على ضرورة وجود نهج رعاية متكامل يشمل كلا الشريكين. ينبغي أن تركز الأبحاث المستقبلية على التقدم في أساليب العلاج ومعالجة الجوانب النفسية والاجتماعية لتعزيز الرفاهية العامة.

الكلمات المفتاحية :العقم، النساء، القدرة على الإنجاب، طرق التشخيص، أساليب العلاج