INFERTILITY: CAUSES, TREATMENTS, AND ALTERNATIVE OPTIONS FOR CONCEIVING A BABY

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ABSTRACT

Infertility affects a significant proportion of fertile couples, with a frequency of one-half to one-sixth of such couples. Infertility is characterized by the inability to conceive after one year of spontaneous, unprotected sexual contact. Although most couples can conceive within six months of such activity, up to 90% of couples achieve conception within a year, with only 5% potentially waiting up to two years. The causes of infertility differ between male and female partners, with male factors accounting for 2.5% to 12% of cases, and female factors ranging from 20% to 70%. There are three typical reasons for infertility, including ovarian factors such as polycystic ovaries (PCO), common risk factors classified into three categories: metabolic (obesity, insulin resistance (IR), gestational and type II diabetes (DM2), and psychological characteristics such as anxiety and depression. Additionally, other factors can contribute to infertility, including fibroids, endometrial/cervical polyps, endometriosis, adenomyosis, tube-ovarian mass, intrauterine and intrapelvic adhesions, septate uterus, and pelvic abscess, as well as chronic pelvic inflammatory disease. The diagnosis of infertility in women involves assessing physical examination, ovulatory function, endometrial biopsy (EBM), ultrasonography, hysterosalpingography, and other diagnostic tests, while in men, it entails semen analyses, testicular biopsy, and other relevant tests. The treatment of infertility can range from simple lifestyle changes and medications such as letrozole, tamoxifen, raloxifene, and clomiphene, either alone or in combination, to more complex assisted reproductive techniques. These methods aim to address the underlying causes of infertility and improve the chances of achieving pregnancy.

Keywords:

Infertility, polycystic ovaries, intrapelvic adhesions, septate uterus, pelvic abscess, semen analyses, testicular biopsy, letrozole, tamoxifen, raloxifene, clomiphene.

INTRODUCTION:

Infertility affects one-fifth to one-sixth of couples of reproductive ages. Infertility can be explained as inability to conceive after a spontaneous unprotected intercourse for 12months [1].The likelihood of conception is determined by the length of sexual exposure, frequency of coitus, and age of the couple. New couples can often conceive after one month of unprotected sexual activity and almost 70% of couples conceive within 6 months of unprotected intercourse whereas 90% of them have probability to conceive within a year and only for 5% couples it might take one and half year or 2 years to conceive [2].

Primary infertility affects couples who have never conceived before. The aetiologies of infertility are equally common in males and females. The three main reasons of infertility—a male factor, ovulatory dysfunction, or tubal-peritoneal disease—are present in the majority of infertile couples [3].

Male factors infertility account for 2.5% to 12%, while female factors account for 20% to 70%. Africa and Central/Eastern Europe had the highest rates of infertility on record. And according to a number of publications, the rates of male infertility in Central and Eastern Europe, Australia, and North America ranged from 4.5 to 6%, 9%, and 8 to 12%, respectively [4].

Numerous scholars have highlighted the common causes of infertility, which can be divided into three categories: (i) ovarian factors, which include polycystic ovaries (PCO); (ii) the common risk factors, which can be divided into: reproductive (infertility, risks associated with pregnancy); metabolic (obesity, insulin resistance (IR), gestational and type II diabetes (DM2); and cardiovascular risk factors; and (iii) psychological features (anxiety and depression) .In addition to (iv) chronic pelvic inflammatory disease, fibroids, anatomical issues, endometrial/cervical polyp, free fluid in the pelvis or abdomen, endometritis, endometriosis, adenomyosis, chocolate cyst, tubo-ovarian mass, intrauterine and intrapelvic adhesions, septate uterus, and pelvic abscess are also present[5] .

Causes of Female infertility:

Any problem that interferes with the fallopian tubes' normal architecture and function and prevents the sperm from meeting the ovum and resulting in conception is the primary cause of fallopian tube-related infertility. Ectopic intrauterine tissue development is referred regarded as a "disease of high social class" since it is more common in developed nations and primarily affects women between the ages of 30 and 40[6][7]. The second most frequent reason for infertility (9.1%) was uterine issues. Infertility is primarily brought on by issues with the uterus's body, namely abnormalities, aberrant uterine placements, inflammation, intrauterine symphysis, endometrial atrophy, and malignant neoplasm [8].

Age of the female is the single most significant factor in determining spontaneous and treatment-related conception, with fertility gradually declining, especially beyond the age of 35[9]. Ovulatory dysfunction and abnormalities in sexual function are common findings in an infertile population [10].

Anovulatory infertility:When follicular development and rupture are compromised, anovulation occurs and the oocyte is not released from the follicle. There are several reasons why anovulation occurs. These include autoimmune, genetic, and other conditions including chemotherapy that can cause intrinsic ovarian failure. Another reason is gonadotrophic regulation-related ovarian malfunction.[11]

One of the main causes of tubal-peritoneal injury is genital infections. Only two microorganisms have been shown to have any direct effects on fertility post-infection, despite the fact that many sexually transmitted diseases (STDs) can be indirectly linked to infertility. These are Chlamydia trachomatis and Neisseria gonorrhoea.[12]

Women suffering from endometriosis experience difficulty in conceiving and maintaining pregnancy.[13] it is known that almost 50% of women with endometriosis are sub fertile[14]

Reduced in-vivo sperm motility is caused by the presence of antisperm antibodies and certain pathogenic substances in cervical mucus. These could be reasons for infertility.[1]

Causes of Male infertility:

The spinal cord and pelvic floor's neurological integrity are crucial for male reproductive function. Patients with neurological damage from illnesses such spinal cord injury (SCI), diabetes mellitus, multiple sclerosis (MS), congenital problems of the spinal cord, trauma, or surgery experience reduced erectile function and ejaculation.[15]

Ejaculatory dysfunction is one of the common cause of infertility in male. The inability to obtain or sustain an erection that is sufficiently rigid for fulfilling sexual interaction is known as erectile dysfunction (ED).[16]

Varicocele defined as an abnormally dilated scrotal veins which effects spermatogenesis, venous reflux and testicular temperature elevation and effects sperm quality and production and testicular dysfunction.[17]

DIAGNOSIS

IN FEMALES

HISTORY AND PHYSICAL EXAMINATION

It is recommended to schedule the first consultation with enough time to gather a complete medical, reproductive, and family history and conduct a thorough physical exam.

The following information should be provided during the consultation: the length of time the individual has been experiencing infertility, as well as any past evaluations or treatments. Additionally, the menstrual history of the patient should be discussed, including their age at menarche, the length and characteristics of their menstrual cycle, the presence of molimina, and the onset and severity of dysmenorrhea.

During the initial consultation, it is important to discuss the patient's pregnancy history, including gravidity, parity, pregnancy outcomes, and any associated complications. The patient should also provide information on their previous methods of contraception and their coital frequency, as well as any sexual dysfunction they may be experiencing. Other relevant medical history that should be discussed include past surgeries, hospitalizations, serious illnesses or injuries, pelvic inflammatory disease, or exposure to sexually transmitted infections. The patient should also be asked about any history of thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, and dyspareunia, as well as previous abnormal pap smears and any subsequent treatment. The patient should provide information on their current medications and allergies, as well as their family history of birth defects, developmental delay, early menopause, or reproductive problems. Additionally, the patient's occupation and exposure to known environmental hazards should be discussed, as well as their use of tobacco, alcohol, and recreational or illicit drugs.[19]

OVULATORY FUNCTION

Assessing ovulatory function can be done through various methods, one of which is examining the menstrual history. Typically, women with ovulation have regular and anticipated menstrual cycles with consistent flow characteristics and accompanying premenstrual symptoms, occurring every 21-35 days[20]

BASAL BODY TEMPERATURE (BBT):

Measuring basal body temperature (BBT) on a regular basis is an easy and cost-effective way to evaluate ovulatory function [21].

OVULATORY FUNCTION THROUGH SERUM PROGESTERONE MEASUREMENTS:

Measuring serum progesterone levels is a dependable and unbiased way to evaluate ovulatory function, provided that it is done at the right time during the menstrual cycle. A progesterone level above 3 ng/mL is a reliable indicator of recent ovulation.[22]

URINARY LUTEINIZING HORMONE (LH):

Commercial ovulation predictor kits that use urine to measure luteinizing hormone (LH) can detect the LH surge in the middle of the menstrual cycle, which occurs a day or two before ovulation. Although urinary LH detection provides indirect evidence of ovulation, it helps to determine the most fertile period, which includes the day of the LH surge and the subsequent day.[23]

ENDOMETRIAL BIOPSY (EBM):

The process of obtaining an endometrial biopsy and examining its histology can reveal the presence of secretory endometrial development, which is a result of the effects of progesterone and indicates the occurrence of ovulation. The traditional histologic criteria used for analyzing the endometrium can help determine its stage of development[24]

OVARIAN RESERVE:

Various tests are employed to evaluate the "ovarian reserve," including measuring FSH and estradiol levels on cycle day 3, conducting a clomiphene citrate challenge test (CCCT), assessing antral follicle count (AFC) in the early follicular phase through transvaginal ultrasound, and analyzing serum antimullerian hormone (AMH) levels. These tests can offer predictive insight in women with a higher risk of diminished ovarian reserve (DOR) [25].

ULTRASONOGRAPHY:

When investigating potential causes of female infertility, ultrasound (US) is often the first imaging method used due to its affordability and ease of use. US can provide an initial evaluation of the structure of the uterus and ovaries, detect conditions such as uterine fibroids and Müllerian anomalies. [26][27]

HYSTEROSALPINGOGRAPHY:

HSG is a less invasive radiographic alternative that involves the transcervical injection of iodinated contrast alongside fluoroscopy [26][27]. Apart from identifying blockages in the fallopian tubes, a hysterosalpingogram (HSG) can also reveal abnormal tube structure, such as peritubal adhesions, hydrosalpinges, or the characteristic nodularity of salpingitis isthmica nodosa. [27]

SONOHYSTEROGRAPHY:

A simple sonohysterography, also known as saline-infusion sonohysterography, can indicate whether the fallopian tubes are open, but it cannot determine which side is affected. If there is fluid present after the procedure, it is a sign of at least one open tube. [28] [29]

MRI AND MR HYSTEROSALPINGOGRAPHY:

MRI stands out as the most reliable method for examining reproductive tract anomalies that may cause infertility, such as uterine fibroids, adenomyosis, and congenital abnormalities [30][31]. MRI is highly beneficial in detecting endometriosis, a condition found in around 30-50% of infertility cases. The hallmark sign of endometrioma on an MRI scan is T2-shading, which has a specificity of over 90%.[32]

Moreover, MRI is a less invasive diagnostic option when compared to the standard gold method of laparoscopy with biopsy. Additionally, it offers the benefit of a wider field of view compared to the typical primary imaging method, transvaginal ultrasound.[32][33]

IN MALE

Deficits in sperm transport or spermatogenesis are the primary causes of male infertility. By carefully analysing semen analyses, gonadotropin levels, and other assays, the diagnosis can be confirmed [34].

1.SEMEN ANALYSES:

These tests can be performed to determine how well the sperm are functioning. The Hemizona Assay (HZA) and the Hamster Egg Penetration Assay (HEPA), which measure sperm's capacity to pierce the egg, can be used to make this determination [35].

2.FSH and LH:

The levels of FSH and LH can be raised in condition called hyper gonadotrophic hypogonadism. High levels of FSH and LH are present in this condition as a result of poor spermatogenesis brought on by testicular failure [36].

3.TESTICULAR BIOPSY:

Testicular biopsies can be carried out for both therapeutic and diagnostic purposes. It is highly advised to undertake testicular tissue cryopreservation (testicular sperm extraction [TESE]) for future intracytoplasmic sperm injection (ICSI), if spermatozoa are available [37]

4.SCROTAL ULTRASONOGRAPHY:

Is essential for measuring testicular size,identifying obstruction-related symptoms such rete testicular enlargement, enlarged epididymis with cystic lesions, and vas deferens absence, and assessing blood reflux in males with varicocele[38].

TREATMENT FOR FEMALE INFERTILITY

LETROZOLE:

In the treatment of anovulatory infertility caused by PCOS, Letrozole is becoming increasinglypopular as the primary therapy, replacing clomiphene.

Letrozole and anastrozole belong to a class of drugs known as aromatase inhibitors. They work by inhibiting the synthesis of estradiol, reducing its feedback on the hypothalamus- pituitary axis, and increasing follicle-stimulating hormone (FSH) production in women with PCOS who have anovulatory infertility. Studies have shown that letrozole, when taken daily for five days at doses of 2.5 to 7.5 mg, and anastrozole at a daily dose of 1 mg for five days, can induce ovulation in women with PCOS. These results suggest that letrozole may be the preferred initial therapy for anovulatory infertility due to PCOS, while anastrozole is generally not recommended for this purpose.

Neither letrozole nor anastrozole have been approved by the FDA for ovulation induction. However, pregnancy and birth registries have reported favorable outcomes for pregnancies resulting from ovulation induction with aromatase inhibitors.[39] In contrast to clomiphene or gonadotropin therapy, aromatase inhibitors promote folliculogenesis by increasing FSH levels while suppressing the production of estradiol, resulting in lower circulating estrogen levels. Theoretically, inducing ovulation with lower levels of circulating estradiol may benefit womenwith a history of estrogen-sensitive malignancies.[40] Women with a history of breast cancer who intend to undergo an IVF cycle may find this effect to be highly beneficial.[41] Aromatase inhibitors could be a valuable alternative monotherapy for women who do not respond to clomiphene.

CLOMIPHENE:

When anovulatory women with PCOS do not ovulate after three escalating doses of clomiphene, alternative medications like letrozole or adjuvants such as metformin or glucocorticoids should be considered. This is due to the low pregnancy rates associated with clomiphene use in many anovulatory women with PCOS.

Developed in 1956, clomiphene is a nonsteroidal triphenylethylene derivative that exhibits both estrogen agonist and antagonist properties, akin to tamoxifen and diethylstilbestrol.

Clomiphene has a half-life of approximately 5 days and is metabolized by the liver into an excretory form that is eliminated through feces. Detectable levels of fecal clomiphene may persist for up to six weeks after discontinuation of the medication. In women with normal menstrual cycles, the administration of 150 mg/day of clomiphene citrate for three days resulted in a 40-50% increase in serum LH and FSH levels.[42]

In women with normal menstrual cycles, the administration of clomiphene citrate for three days led to a significant increase in LH pulse frequency, rising from 3.3 to 6.8 pulses per eighthours. The mechanism of action of clomiphene is thought to involve effects on the hypothalamus, as evidenced by this increase in LH pulse frequency.

In addition to its hypothalamic site of action, clomiphene has biological effects on the pituitary, ovary, endometrium, and cervix. When given to hypoestrogenic women receiving exogenous estrogen, clomiphene can cause endometrial degeneration.[43] Clomiphene has been shown decrease the amount and quality of estrogen-induced cervical mucus. [44,45] Although clomiphene can induce ovulation, its adverse effects on the endometrium and cervix may decrease the pregnancy rate per ovulatory cycle.

Clomiphene Plus Glucocorticoid Induction of Ovulation

The term "clomiphene resistance" refers to patients with PCOS who did not ovulate despite taking standard doses of clomiphene.

To improve ovulation in women with clomiphene resistance, a combination therapy of clomiphene and dexamethasone can be effective, but the infertility work-up should be assessed beforehand to rule out other factors. Randomized clinical trials have shown that this combination increases the chances of ovulation and pregnancy compared to using clomiphene alone. [46,47]

Doctors often advise their patients to take dexamethasone at night to reduce the morning surge of corticotropin-adrenocorticotropic hormone (ACTH), which increases the productionof adrenal androgen. If clomiphene (100 mg daily for 5 days) and dexamethasone fail to induce ovulation, a 150 mg daily dose of clomiphene for cycle days 3 to 7 with dexamethasone may be recommended. If this regimen also fails to induce ovulation, alternative ovulation induction methods such as weight loss, gonadotropin injections, laparoscopic ovarian drilling, or IVF should be considered by the patient

Contraceptive Pretreatment:

An elevated baseline level of testosterone in the bloodstream can be a risk factor for clomiphene resistance in terms of ovulation failure. To counter this, administering estrogen-progestin before a cycle of clomiphene could potentially increase ovulation rates prior to starting the clomiphene cycle by reducing circulating testosterone levels.

Two clinical studies, including a small case series and a randomized trial, have reported that administering continuous estrogen-progestin contraceptive pills for 2 months before starting clomiphene treatment may decrease circulating testosterone and enhance ovulation and pregnancy rates in PCOS women who previously failed to ovulate with clomiphene 150 mg daily for 5 days.[48]

Clomiphene and Nonclassical Adrenal Hyperplasia:

Studies recommend the administration of glucocorticoids, specifically prednisolone at a daily dosage of 5 to 7.5 mg, to infertile anovulatory women with nonclassical adrenal hyperplasia (NCAH) caused by mutations in 21-hydroxylase to induce ovulation. However, some women with long-standing NCAH also exhibit polycystic ovarian morphology on ultrasound, indicating ovarian hyperandrogenism. In such cases, clomiphene alone or in combination with glucocorticoids may be utilized to induce ovulation and achieve pregnancyin infertile women with NCAH. [49,50]

Clomiphene Plus Gonadotropin Induction of Ovulation:

To induce ovulation in women who do not ovulate with conventional doses of clomiphene citrate (CC), gonadotropin injections can be given alongside the CC therapy. This approach offers the advantage of reducing the number of gonadotropins needed during each cycle to stimulate ovulation. The initial rise in follicle-stimulating hormone (FSH) and luteinizinghormone (LH) induced by CC increases the responsiveness of the follicles to gonadotropin injections. Typically, CC is administered at a dosage of 100 to 200 mg per day for 5 days, followed by the initiation of FSH or LH-FSH injections. Research indicates that this protocol reduces the required gonadotropin dosage by 50% to trigger ovulation. [51,52]

Clomiphene and Metformin:

If metformin is used as monotherapy, progesterone levels can be checked periodically on the appropriate days to confirm ovulationor the patient can maintain a basal body temperature (BBT) chart. If ovulation has not occurred after 5 to 10 weeks of metformin monotherapy, it can be used in conjunction with clomiphene (50 mg/day for five days). Metformin can be discontinued if the patient becomespregnant. Some doctors have prescribed metformin, a category B medication for pregnant women, to treat gestational diabetes and type 2 diabetes during pregnancy.

Prior to initiating metformin treatment, the FDA recommends testing the patient's serum creatinine levels and ensuring that they are below 1.4 mg/dL, despite the rarity of metformin-induced lactic acidosis. Along with clomiphene and gonadotropins, other insulin sensitizers have the potential to aid in ovulation induction.

Regarding the relative effectiveness of metformin versus clomiphene, clinical investigations have revealed contradictory findings.

Most of the extensive clinical trials have shown that metformin and clomiphene used alone have similar effectiveness in inducing ovulation in women with PCOS. However, clomiphene has shown higher ovulation, conception, and birth rates per cycle compared to metformin. Ina particular trial, 626 women with anovulatory infertility caused by PCOS were given either clomiphene alone, metformin alone, or a combination of clomiphene and metformin.[53]

During the trial, the group of women who were treated with a combination of clomiphene and metformin had a higher rate of live births at 27%, compared to the clomiphene-only group which had a rate of 23%, and the metformin-only group which had a much lower rate of 7%. However, some studies conducted by other researchers have shown that the rates of conception when using either clomiphene or metformin alone are similar.[54]

In cases where a woman with PCOS-induced anovulatory infertility has attempted to conceive using clomiphene, treatment with a combination of clomiphene and metformin is less likely to result in success compared to FSH therapy or ovarian drilling.[55]

Clomiphene versus Tamoxifen or Raloxifene for Ovulation Induction

Clomiphene, tamoxifen, and raloxifene are estrogen agonists and antagonists that exhibit varying degrees of agonist or antagonist action in different organs. In a trial where patients were randomly assigned, 371 anovulatory women with PCOS were treated with either 100 mg of clomiphene daily or 20 mg of tamoxifen daily for five days. The ovulation rate was 64%for the clomiphene group and 52% for the tamoxifen group (P=.01), while the pregnancy rates were 19% and 11%, respectively (P=.04). [56]

TREATMENT FOR MALE INFERTILITY:

Male infertility can be treated with various medications, each of which is chosen based on the specific cause of infertility.

Some common medications include

1. Clomiphene citrate, which is used to increase sperm production in men with low testosterone levels
2. Human chorionic gonadotropin (HCG), used to stimulate the testicles to produce more testosterone and sperm
3. Tamoxifen, used to treat idiopathic oligozoospermia, a condition characterized by low sperm count
4. Anastrozole, which is used to treat elevated levels of estrogen in men that can impact sperm production.
5. Coenzyme Q10 is not a medication that requires a prescription, but rather a molecule produced by the human body through diet or supplementation. It is also a potent antioxidant that has demonstrated positive effects on various health issues, including male fertility.
6. Studies have revealed that in men with irregular sperm parameters, the use of Coenzyme Q10 can enhance both the quality and movement of sperm. Additionally, it may have a beneficial impact on men who have pyospermia, a condition characterized by an excessive amount of white blood cells in semen.[57]

Surgical Procedures:

Male infertility can be addressed through various surgical procedures, which are selected based on the underlying cause of infertility. Some common surgical treatments include

1. **Vasectomy Reversal**: a procedure that involves reconnecting the tubes responsible for transporting sperm from the testicles to the urethra after a vasectomy
2. **Varicocelectomy**: which involves correcting enlarged veins in the scrotum that can impact sperm production and quality
3. **Epididymal Sperm Aspiration (ESA)**: a method for removing sperm directly from the epididymis, a small duct that stores and transports sperm
4. **Microsurgical Testicular Sperm Extraction (Micro-TESE)**: a procedure that searches for sperm in the testicles either due to blockages in the vas deferens or low sperm production.[58]
5. **Intrauterine Insemination:** is a fertility procedure that involves introducing washed and processed sperm into the uterus of the female partner. The viable sperm is concentrated before being injected through the use of a thin tube, known as a catheter. This method aims to increase the chances of fertilization by getting the sperm closer to the egg at the time of ovulation.

6. **In vitro fertilization:** is a treatment option for male infertility that encompasses multiple stages. Firstly, the female partner undergoes stimulation of the ovaries to retrieve eggs. These eggs are then combined with sperm in the laboratory, where fertilization takes place. The growth and development of the resulting embryos are closely monitored, and a single embryo is chosen for transfer into the uterus of the female partner by a physician.
7. **Intracytoplasmic Sperm Injection (ICSI):** is a specialized form of in vitro fertilization (IVF) that is specifically designed for men with low sperm count. The procedure involves the isolation of a single healthy sperm by an embryologist, followed by the injection of that sperm into each egg in the laboratory. This method has proven successful in enabling many men with extremely low sperm count to father healthy children, and is considered an effective treatment option for infertility.

8. **Donor sperm**: The use of donor sperm can be a solution for men who have sperm counts that are insufficient for conception. Additionally, some men choose this option to prevent the transmission of a genetic condition to their offspring.[59]

9. **Lifestyle changes**: In certain situations, modifications to one's lifestyle can enhance fertility. Such changes can include weight loss, cessation of smoking, and reduction in alcohol and drug consumption.[60]

DISCUSSION:

Infertility is a widespread concern impacting a significant number of couples worldwide. It encompasses various factors contributing to its complexity, including both male and female causes such as ovarian dysfunction, tubal-peritoneal diseases, genetic predispositions, and environmental influences (1).Accurate diagnosis is paramount in effectively managing infertility cases. This involves thorough medical history-taking, physical examinations, and a range of diagnostic tests such as hormonal assessments, ultrasound imaging, and histological evaluations, enabling a comprehensive assessment of the underlying causes (2).Treatment options for infertility are diverse and tailored to individual patient needs. Pharmacological interventions like Letrozole and Clomiphene are commonly utilized to address ovulatory dysfunction in females. Meanwhile, surgical procedures like Vasectomy Reversal and Intrauterine Insemination offer targeted solutions for specific conditions (3).Future research endeavors in infertility treatment focus on exploring the efficacy of emerging therapies, understanding the impact of lifestyle modifications on fertility outcomes, and investigating the long-term implications of certain treatment approaches (4).Effective patient counseling and informed decision-making are integral aspects of infertility management. Healthcare providers play a pivotal role in guiding patients through treatment options, addressing potential risks, and establishing realistic expectations, fostering a collaborative patient-provider relationship (5).

CONCLUSION:

Infertility represents a multifaceted challenge with diverse causes and treatment modalities. By comprehensively addressing both female and male infertility, healthcare professionals can better navigate this complex issue and enhance patient outcomes.

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