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REVIEW

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Infertility diagnosis and management

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Abstract

Background One of the most stressful problems for married couples is infertility, which is a widespread health issue. It has been defined as a profound life-changing problem that comes with severe psychological stress despite the fact that it is not fatal. The rate of infertility among couples is gradually rising due to postponing childbearing, which is brought on by several social and economic causes.

Main body Depending on the cause, the length of the couple's struggle, and the ages of the partners, infertility can be treated medically, surgically, or with modern reproductive assistance (in vitro fertilisation, intrauterine insemination, intracytoplasmic sperm injection, and nanotechnology). Fertility issues can be a stressful circumstance in a person's life with serious psychological repercussions. Hypogonadotropic hypogonadism, hyperprolactinemia, ciliary disorders, cystic fibrosis, infections, systemic diseases, and diseases connected to lifestyle are the factors that impair fertility in both sexes. Female infertility may be caused by premature ovarian insufficiency, polycystic ovary syndrome, endometriosis, uterine fibroids, and pelvic inflammatory disease. Testicular and post-testicular deficits can cause male infertility. Other potential contributing factors include consanguinity, endocrine disrupting substances, and the observed semen reduction throughout time.

Conclusion One in eight females between the ages of 15 and 49 receives assistance with conception. Although success rates vary by age and diagnosis, many couples receiving treatment for infertility can achieve their fertility objectives with the help of a precise diagnosis, efficient therapy, and shared decision-making. The term "assisted reproductive technology" can facilitate egg fertilisation and aid implantation of the fertilised egg in the uterine lining.

Keywords Infertility, Causes of female and male infertility and "assisted reproductive technology" (ART) for infertility

1 Background

The inability to become pregnant after participating in regular, protected sexual activity for at least a year is a sign of infertility, a disease of the male or female reproductive system. After a year of unprotected sexual activity, infertility is the inability to get pregnant [1]. In the USA, 10–15% of married couples have infertility [2]. Male and female spouses both contribute equally to the infertility, with the other factors being a result of their joint efforts [3]. The motivation for having children is the formation of a new family unit which essential to a person's instinct for survival [4]. Having fertility problems can be a stressful situation in a person's life with negative psychological effects. The qualified clinician should be aware of and comprehend the heavy burdens and frustrated demeanour of the infertile person. Most adults are motivated to discuss their sexual problems, issues, and behaviours if the interview is conducted in a polite, confidential, professional, and non-judgmental manner. Throughout the past few decades, significant advancements have been made in the field of male infertility. Procedures for diagnosis and treatment have both made important related improvements. Due to the fact that many infertile couples suffer from many causes of infertility, you will likely both need to see a doctor [4]. Male infertility is most frequently brought on by issues with the ejection of semen, a lack of sperm or low sperm counts, or irregular sperm shape (morphology) and

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motility (motion). Women who are infertile can develop a variety of diseases that affect their ovaries, uterus, fallopian tubes, and endocrine systems, among other organs. Primary or secondary infertility is both possible. If at least one prior pregnancy was successful, a person has secondary infertility, whereas primary infertility is when a pregnancy has never been successful. When a couple regularly engages in unprotected sexual activity yet is unable to conceive, every seventh couple may have trouble getting pregnant. 84% of couples who engage in regular, unprotected intercourse will spontaneously become pregnant (every two or three days) within a year. For couples who have spent more than three years attempting to conceive, the likelihood of becoming pregnant naturally in the following year is 1 in 4, or less [1].

2 Main text

2.1 Types of infertility

Many factors can contribute to infertility. For one in four marriages, the reason is unknown.

2.1.1 Female infertility

The female is to blame for infertility in roughly 45% of infertile marriages. Male factor infertility affects 30% of cases, while the remaining 25% go undiagnosed.

- Fertilised oocytes (10–15%) split, but fail to implant.
- Implanted ova (42%) are successful in suppressing the subsequent menstrual cycle.

- Women have abortion (24%) in 4th week of pregnancy [5, 6].

2.1.1.1 Ovulation issues may arise from

- *Thyroid issues associated with polycystic ovarian syndrome (PCOS)*: Ovulation premature ovarian failure, in which the ovaries cease to function before the age of 40, can be avoided by both an overactive thyroid gland and an underactive thyroid gland.
- *Scarring from surgery*: During pelvic surgery, the fallopian tubes, which join the ovaries to the womb, may be hurt or scarred. Moreover, some cervical surgeries shorten the womb's neck or leave scars behind (the cervix).
- *A cervical mucus issue*: cervix's mucous thins during ovulation to make it easier for sperm to get through. Conception may be more difficult if there is a mucus issue.
- *Fibroids*: Fertility may be impacted by non-cancerous growths called fibroids which develop in or near the uterus. They may occasionally stop a zygote from adhering to the fallopian tube or uterus.
- *Endometriosis*: Little fragments of the endometrium, the lining of the womb, begin to grow in other locations, such as the ovaries, in endometriosis. Infertility issues may result from this harm to the fallopian tubes or the ovaries.
- *Inflammatory illness of the pelvis*: is an infection of the upper female genital tract, which includes the ovaries, fallopian tubes, and wombs known as pelvic inflammatory disease (PID). Often, a sexually transmitted infection is the culprit. PID has the potential to scar and injure the fallopian tubes, effectively blocking an egg's descent into the womb.
- *Sterilisation*: If a woman decides she does not want to have any more children, she may elect to be sterilised. To prevent an egg from entering the womb, the fallopian tubes are blocked during sterilisation. Sterilisations are rarely reversible, and even if they are, you might not be able to conceive.

-*Medicines and drugs*: Your fertility may be impacted by the side effects of certain medications and pharmaceuticals, including the following:

- N*on-steroidal anti-inflammatory drugs (NSAIDs)*: It may be more challenging to get pregnant if you use NSAIDs like ibuprofen or aspirin frequently or in excessive doses.
- *Chemotherapy*: Ovarian failure is a side effect of several chemotherapy drugs that prevents your ovaries from functioning properly. Anti-neuroleptic drugs and antipsychotic drugs, which are frequently prescribed to cure schizophrenia, can occasionally result in infertility or missed periods.
- *Spironolactone*: a medication used to treat oedema (fluid retention); after stopping spironolactone, in about two months, fertility should resume. Illicit substances like marijuana and cocaine can have a major negative impact on fertility and make ovulation more challenging.

2.1.1.2 Fallopian tubes problems Infection or injury to the fallopian tubes is one of the most frequent reasons of infertility in women. The majority of the time, one or both tubes may be obstructed, preventing the movement of eggs, spermatozoa, or embryos from the ovary to the uterus. Harm to the mucosal lining, partial obstruction, and adhesions are also frequent. The latter are distinguished by tissue strands that emerge from sick places and maintain the tubes' stability and ability to move, such as when picking up an ovum, for example [7].

2.1.1.3 Uterine problems While a woman is pregnant, the uterus, also known as the womb, is where the baby develops. Bleeding between cycles or after intercourse may be the first indicator of uterine problems. Uterine difficulties are ailments that impact the uterus or any other portion of your reproductive system. There are several potential causes, including hormonal imbalances, cancer, fibroids, polyps, and infections during pregnancy. Uterine fibroids, endometriosis, uterine prolapse, and uterine tuberculosis are a few frequent uterine conditions. In two more uterine conditions, tissue that ordinarily borders the uterus grows in an unnatural location. It expands external to the uterus in endometriosis. It develops in the outer walls of the uterus during adenomyosis. Painkillers might be useful. In addition, there are surgical and hormonal therapies.

2.1.2 Male infertility

30% of infertile couples caused by male infertility. Most often, oligospermia, or a lack of spermatozoa in the semen or sperm of poor quality or motility, is the issue. Surgery for azoospermia, or no sperm production, is far less prevalent [7].

2.1.2.1 Semen and sperm Low-grade sperm, the fluid that contains sperm that is ejaculated while having sex, is a common factor in male infertility. Among the potential causes of anomalous semen are: not enough sperm. Sperm that are not moving properly or that are very low in number will make it more difficult for them to swim to the oocyte. Sometimes aberrant sperm have odd shapes, which makes it more difficult for them to migrate and fertilise an oocyte. There are many unexplained cases of anomalous semen. Although there is a connection between elevated scrotal warmth and decreased semen quality, it is unknown whether donning baggy underwear increases fertility.

2.1.2.2 Testicles Sperm are produced and kept in the testis. The quality of the semen may be significantly impacted by damage to them. This might happen if testis are infected, have cancer, have undergone surgery, have a congenital deformity, or have been injured. It can also happen if one or both of the testis have not descended into the scrotum.

2.1.2.3 Sterilisation Some men decide to undergo a vasectomy. It entails severing and closing up the vas deferens, which transports sperm from your testicles, to ensure that your semen is devoid of sperm. It is possible to undo a vasectomy; however, this rarely results in success.

2.1.2.4 Ejaculation disorders Some men may have trouble passing semen during ejaculation (intercourse) due to ejaculation issues.

2.1.2.5 Hypogonadism Low levels of testosterone, the male sex hormone essential for the production of sperm, are referred to medically as hypogonadism. Drug abuse, cancer, or the rare condition known as Klinefelter syndrome (which contains an extra female chromosome) could all be to blame.

2.1.2.6 Medicines and drugs Many types of medicines may cause infertility issues. These include:

- *Sulfasalazine*: is an anti-inflammatory medication used to treat conditions like rheumatoid arthritis and Crohn's disease. It may momentarily suppress sperm counts, but as soon as stop using it, they should start to rise again.
- *Anabolic*: Illegal use of anabolic steroids is common to increase sports performance and muscle mass; prolonged use of these drugs can lower sperm quality and motility.
- *Chemotherapy*: therapies using herbs and some herbal medicines, such as root preparations of the Chinese herb Tripterygium wilfordii, have been demonstrated to affect testicle size or sperm production. Chemotherapy drugs sometimes cause a considerable reduction in sperm production.
- *Illegal drugs*: Semen quality may be impacted by drugs like cocaine and marijuana.

2.1.3 Unexplained infertility

When neither spouse can pinpoint the source, this is the situation. See your doctor about the next steps if the root of your fertility issues has not yet been identified. The National Institute for Health and Care Excellence (NICE) recommends making IVF therapy available to women with unexplained infertility who have not conceived after two years of engaging in frequent unprotected sexual contact. More information on unexplained infertility can be found in the NICE recommendations.

2.2 Diagnosis

2.2.1 Female examination

Questions about menstruation and related factors, marriage and childbirth histories, and high-risk factors that may affect the fallopian tube or pelvic environment should all be carefully questioned in order to ascertain

the likelihood of ovulatory dysfunction or aberrant pelvic factors [8].

2.2.1.1 Physical examination In both general and gynaecological exams, take the following into consideration:

- A general assessment primarily focuses on a patient's growth and nutritional state, including thyromegaly, skin changes, secondary sex features, weight, height, and body fat distribution.
- It is necessary to confirm the following. The position, size, texture, shape, and mobility of the uterus, the pubic hair pattern, the size of the clitoris, the presence of abnormal vaginal secretion, whether the cervix is smooth without abnormal secretion, whether the accessory area is thickening, massing, or tender, and whether the aforementioned symptoms are noticeable [14].

2.2.1.2 Ovulatory function Up to 40% of female infertility is caused by ovulatory disorder, which will be found in 15% of all infertile couples [8]. Ovulatory dysfunction is most frequently brought on by polycystic ovarian syndrome, obesity, weight gain or loss, intense activity, thyroid issues, and hyperprolactinemia. Even though a woman's cycle usually lasts longer than 25 days, irregular menstrual cycles, periods that last less than 21 days or more than 35 days, or complaints of abnormal uterine bleeding or amenorrhea may cause ovarian cancer to be suspected [9]. Usually, ovulation happens 14 days before to the start of menstruation. A postovulatory serum progesterone level that is measured in the anticipated midluteal phase, roughly one week before to the anticipated menses, may be used to identify ovulation in cases when the menstrual history is lacking or unclear. Seventy per cent of women with anovulation have polycystic ovarian syndrome (PCOS), which is the condition's most prevalent cause [10]. Along with PCOS, obesity has been linked to anovulation; women with a body mass index (BMI; calculated as weight in kilogrammes divided by height in metres squared) greater than 27 are at a higher risk of anovulatory infertility than women with a BMI in the normal range (relative risk: 3.1 [95% CI 2.2–4.4]; absolute rates were not provided in the American Society for Reproductive Medicine guideline) [11]. Additional causes include thyroid illness (2–3%), pituitary disease (13%), increased androgens from an adrenal tumour or hyperplasia (2%), idiopathic chronic ovulation (7–8%), and functional hypothalamic amenorrhea (induced, for example, by underweight, eating disorders, or extreme exercise). Anovulatory infertility is more frequent in patients with eating disorders than in women without eating disorders (16.2% vs. 5.6%; $n=271$) [12, 13]. Any of the following techniques may be used to assess ovulatory function:

- A woman's menstrual history can be sufficient.
- Repeated measures of basal body temperature (BBT) offer an easy and affordable way to assess ovulatory function. The seven days before the mid-cycle surge in BBT are when fertility is at its peak in cycles being tracked by BBT. Women with more modest ovulatory failure may be identified by (10 days of temperature elevation). The test can get boring and is unable to accurately pinpoint the ovulation time. As a result, for the majority of infertile women, BBT is no longer regarded as the best or recommended tool for evaluating ovulatory activity [8].
- Serum progesterone levels provide a reliable and unbiased evaluation of ovulatory function if they are measured at the appropriate time in the cycle. Given the range of natural variation in ovulatory cycles (e.g. cycle day 21), a blood progesterone measurement should normally be performed around a week before the anticipated start of the following menses rather than on any specific cycle day. Progesterone concentrations greater than 3 ng/mL provide suspect but reliable evidence of recent ovulation. The criterion is unreliable because of the pulsatile nature of corpus luteum progesterone secretion and the potential for up to sevenfold fluctuations in serum concentration over a few hours, even though higher threshold values (such as R10 ng/mL) have frequently been used to evaluate the quality of luteal function [8].
- Several commercial "ovulation predictor kits" that measure urinary luteinising hormone (LH) can be used to identify the mid-cycle LH spike, which takes place one to two days before ovulation. Urinary LH detection is an indirect indicator of ovulation and aids in identifying the time of greatest fertility, which is the day of the LH surge and the two days that follow. Particularly when the test is performed on midday or evening urine samples, results frequently closely match the peak in serum LH. Accuracy, usability, and dependability of products varies, and testing can result in both false positive and false negative results [8]. Progesterone-induced secretory endometrium can be seen during endometrial biopsy (EBM) and histology, which supports ovulation. The lack of precision and accuracy, as well as the inability to distinguish between fertile and infertile women, has led to the conclusion that histologic endometrial dating is not a valid diagnostic tool. Therefore, it is no longer recommended to test an infertile woman's ovulatory or luteal function, and endometrial biopsy should

only be carried out when a specific endometrial condition (such neoplasia or chronic endometritis) is strongly suspected [8]. Transvaginal ultrasonography has the ability to count the growing follicles, count their size, and count putative ovulation and luteinisation indications. The abrupt collapse of the pre-ovulatory follicle, loss of clearly defined follicular boundaries, appearance of internal echoes, and a rise in the volume of the cul de sac fluid are some of these symptoms. The method should typically only be used for women in circumstances where simpler approaches are unable to offer the essential information due to the cost and practical challenges involved [8].

- TSH and prolactin measurements in the serum can identify hyperprolactinemia and/or thyroid problems, which may require specialised care [8].
- In amenorrheic women, measurements of serum follicle-stimulating hormone (FSH) and estradiol can distinguish between those who have hypothalamic amenorrhea (low or normal FSH, low estradiol), which will require exogenous gonadotropin stimulation to induce ovulation, and those who have ovarian failure (high FSH, lowest estradiol), who may be candidates for oocyte donation [8].

2.2.1.3 Ultrasound examination

- *Pelvic ultrasound examination*: This requires placing a particular instrument into the vagina as opposed to a typical, external ultrasonography. It projects an image of the uterus and other reproductive organs on a screen using high-frequency sound waves. The doctor can then spot any structural issues or fibroids that might be preventing pregnancy. This is normally done two weeks prior to the patient's period and is not [15].
- *Hysterosalpingography (HSG)*: A radiopaque dye is injected into the uterine cavity via a catheter during a fluoroscopic examination to evaluate the morphology of the cavity and the patency of the fallopian tubes. The test is typically planned for the time period right after monthly menstruation and before ovulation. HSG should not be done if there is an adnexal tumour, pelvic inflammatory disease, a history of ectopic pregnancy, an allergy to a radiocontrast dye, or an iodine allergy. During an HSG, congenital anomalies, intrauterine polyps, submucous leiomyomas, surgical alterations, and synechiae may be discovered. Among the tubal abnormalities are peritubal adhesions, polyps, hydrosalpinx, salpingitis isthmica nodosum, and proximal or distal tubal blockage [15].
- *Sonohysterography (SHG)*: Investigations using SHG can be conducted to look into issues like irregular uterine bleeding, infertility, and recurrent miscarriage. SHG can be used to examine the uterus's architecture. This can be done in women who have uterine congenital abnormalities (birth defects), prior to and during uterine surgery, or to find issues that develop later in life, like polyps or possible scar tissue inside the uterus. SHG might also be used to investigate uterine anomalies discovered during a standard ultrasound. SHG is often performed following the end of the menstrual cycle. It may be done at any time in women who are not menstruation (such as those taking drugs to suppress the menstrual cycle, postmenopausal women, etc.). An ultrasound examination utilising a probe inserted in the vagina starts the process. The uterus is then filled with sterile saline (salt water) using a thin catheter that is inserted via the cervix using a speculum. The uterus is filled with saline solution, which helps define the uterine walls and cavity. This reveals abnormalities in the uterus, such as fibroids, polyps, or scar tissue [16].
- *Laparoscopy*: In this minimally invasive procedure, your fallopian tubes, ovaries, and uterus are examined by inserting a thin viewing equipment through a small incision made beneath your navel. Endometriosis, scarring, blockages or abnormalities of the fallopian tubes, as well as issues with the ovaries and uterus, may all be discovered during a laparoscopy [17].

2.2.2 Protocols used for evaluation of infertile males

60% of cases involving couples of reproductive age who are experiencing fertility-related problems are either directly or indirectly related to male infertility [18, 19]. Male infertility assessment is frequently undervalued or delayed. The effectiveness, danger, and expense of following therapy are all improved with a coordinated evaluation of the infertile male utilising established protocols. The ability to recognise and treat reasons of male infertility that were previously incurable has been made possible by recent developments in assisted reproductive techniques (ART). It is crucial that patients are correctly identified and evaluated in order to make the best use of the techniques that are currently available and enhance therapeutic outcomes. In a perfect world, this preliminary evaluation would also be affordable and available. We provide information on the wise use of current diagnostic techniques and better understand the aetiology of the best appropriate treatment for the existing disease by providing a practical description of the main features of male infertility evaluation [19]. A male's initial evaluation

is based primarily on histology, a physical examination, and sperm analysis. Semen analyses and acquiring a reproductive history, including a sexual history, are important procedures that are generally accepted. The following details should be included in the reproductive history, according to the ASRM [19]: Sexual history (including STDs), sexual frequency and timing, length of infertility, prior fertility, childhood ailments, previous surgeries, drugs, and allergies, as well as exposure to gonadotoxins, such as heat and chemical toxins, are all factors [19, 20].

2.2.2.1 Physical examination Secondary sexual features such skeletal proportions, hair pattern, and muscular mass are observed during a thorough physical assessment. The genitalia should receive special consideration with regard to testicular size and the disparity in development between the two sides. The vas should be easily perceptible and the epididymis should not be swollen or indurated. Congenital vas absence is typically identifiable and may be linked to renal abnormalities. When a patient is standing, large varicoceles may be readily visible along the spermatic cord, whereas minor ones may only be perceptible during Valsalva. Varicoceles should easily decompress when the patient is supine if there is no obstruction to internal spermatic venous drainage in the retroperitoneal region. Prostate needs to Varicoceles should be simple to decompress when the patient is lying supine if there is no obstruction to internal spermatic venous drainage in the retroperitoneal region. A little, non-tender prostate should be palpable in the rectal area. Unsuitable urethral meatus placement or stenosis may prevent proper semen deposition in the vagina [14].

2.2.2.2 Laboratory examination

- *Hormonal examination*: To ascertain the general hormonal system balance and the precise stage of sperm production, measure the levels of testosterone and FSH (follicle-stimulating hormone). If preliminary testing reveals a need for them, additional hormonal tests, such as those for prolactin and serum LH, may be performed [20].
- *Seminal examination*: Semen analysis should be performed 2–3 times for the male partner of an infertile relationship in order to establish baseline data. The test needs to be given every time at the same time, 2–7 days after ejaculation. The result and the clinical characteristics should be carefully analysed together. Any individual can go through a wide range of changes. The range of each measure is therefore simply used as a guide when evaluating the fertility of males, and it is not the main determinant in diagnosing infertility. Males with results over the bottom bound of the reference range are not strictly sterile. In addition, each laboratory should define its own reference range based on sperm concentration in consideration of the variations between areas or laboratories. The following categories apply to individuals with oligozoospermia:

  - The mild-to-moderate level of sperm concentration is defined as the range of 5–15 106/mL for 2–3 consecutive standard semen analyses.
  - Serious level: 1–106 sperm per millilitre of semen for 2–3 consecutive standard semen examinations. (3) The sperm concentration reaches a severe level of less than 1 106/mL after two to three consecutive standard semen examinations.
  - Cryptozoospermia is a condition in which spermatozoa are only visible in sediment pellets during centrifugation and not in fresh semen samples [19, 21, 22].

2.2.2.3 Ultrasound examination In cases of male infertility, ultrasound is typically always the first imaging test performed. Evaluation aims to determine testicular morphology, efferent duct patency, and prostatic abnormalities. Moreover, erectile dysfunction may be evaluated [23].

- *Scrotal ultrasound*: The examination makes use of a high-frequency (7–12 MHz) linear array transducer that is long enough to measure the testis longitudinally. The patient is examined while lying flat. The testes should be routinely evaluated in orthogonal transverse and longitudinal planes, as well as through colour Doppler evaluation and volume measures. The formula for measuring volume is typically: length*height*width*0.51. In general, a single testicular volume of 12–15 ml and a combined volume (both testes) > 30 ml are regarded as normal [18].
- *Transrectal ultrasound*: Transrectal ultrasound, which provides high-resolution imaging of the prostate, seminal vesicles, and vas deferens, is the advised method for identifying congenital and acquired abnormalities associated in the pathophysiology of obstructive azoospermia. The terminal vas deferens, seminal vesicles, ejaculatory duct, and prostate are all thoroughly examined in the axial and sagittal planes [23].
- *Moderate and dynamic colour Doppler penis ultrasound*: Penile ultrasonography is utilised to identify the underlying physical causes of erectile dysfunction. They include difficulties with the venous occlusive system, artery input, and anomalies in the

penile's structure. Due to the small risk of priapism, informed consent must be obtained before to intracavernosal prostaglandin injection [23].

- *Magnetic resonance imaging techniques (MRI)*: help detect prostatic cysts and evaluate the vas deferens, seminal vesicles, and ejaculatory ducts. This makes triplanar T2-weighted spin echo imaging with [long repetition time (TR)/long echo time (TE)] the ideal method and short TR/short TE T1-weighted turbo spin echo images with a slice thickness of 3–4 mm used to get high-resolution images of the triplanar [20, 23].

2.2.3 Other examinations

- After an orgasm, checking your pee. With the exception of people who have hypoplasia of the bilateral spermaducts or clinical signs of hypogonadism, it applies to people who do not excrete semen or who have post-orgasmic semen volumes of less than 1 mL.
- Anti-sperm antibodies in seminal plasma should only be used as a reference for immunological infertility and not as a stand-alone criterion.
- Genetic testing: Patients with severe oligozoospermia or azoospermia may benefit from Y chromosome microdeletion testing and karyotype analysis. Patients whose azoospermia is accompanied by unilateral or bilateral spermaduct agenesis may benefit from CFTR gene testing. Patients with suspected Kallmann syndrome may benefit from Kal gene testing.
- Patients with hyperprolactinemia and insufficient gonadotropin secretion can benefit from imaging assessment of the hypothalamus-pituitary area.
- Diagnostic testicular biopsy is advised for individuals with azoospermia to assess the testis' capacity to generate sperm and determine if their condition is obstructive or non-obstructive [14]. WHO 2021's minimum amount for procreative semen:

Volume of semen (mL):	**1.4 (1.3–1.5)**
Total number of sperm (106 per ejaculate):	39 (35–40)
The motility (%)	42 (40–43)
Progression of motility (%)	30 (29–31)
Motility that does not advance (%)	1 (1–1)
Immobile sperm (%)	20 (19–20)
Energy (%)	54 (50–56)
Stander forms (%)	(3.9–4)

2.3 Infertility treatment

Infertility treatment is dependent on understanding the causing of infertility, the time which couple spent with infertility, the age of partners. Certain infertility causes are unfixable. Couples can frequently still conceive even when a spontaneous pregnancy does not occur by using assisted reproductive technology. Treatment for infertility may require tremendous time, effort, and financial obligations [24].

2.3.1 Medical treatment of infertility

Among the drugs used by both men and women include gonadotropins, follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH) analogues, aromatase inhibitors, and metformin [24].

2.3.1.1 Clomiphene citrate By stimulating the pituitary gland to generate more FSH and LH when taken orally, this medication promotes ovulation by encouraging the development of an ovarian follicle that contains an egg. In most cases, this is the first line of treatment for women under the age of 39 without PCOS. Pituitary gland in the brain secretes more follicle-stimulating hormone (FSH) and LH when clomiphene is taken (luteinising hormone). This causes the ovarian follicle to develop more quickly, which starts the ovulation process [25]. Some side effects of Clomiphene include:

- Flushing (extremely common)
- "Mittelschmerz" (pain and heightened sensitivity associated with ovulation)
- blurred, double, or "traces" vision (a complication which may cause treatment to be discontinued)
- Sadness (requiring discontinuation in severe cases)
- Nausea
- Breast sensitivity
- Headache
- Vaginal aridity
- Clomiphene may have a negative effect on oestrogen production in 20% of patients, which inhibits the uterine lining from thickening at the proper period and causes greater sensitivity, commonly known as "mittelschmerz".
- Double, fuzzy, or "traces" vision (a complication which may cause treatment to be discontinued) Moodiness (which, in extreme circumstances, requires abstinence) (requiring discontinuation in severe cases). Only one egg is ovulated during a typical menstrual cycle. The ovaries frequently generate two or three eggs per cycle when clomiphene is used. Clomiphene is taken orally for five days,

and only the month it is administered has any effect [25].

2.3.1.2 Gonadotropins These intravenous therapies encourage the ovary to release many eggs. Human menopausal gonadotropin, often known as HMG (Menopur), and FSH are examples of gonadotropin medicines. Human chorionic gonadotropin (Ovidrel, Pregnyl), a different gonadotropin, is used to develop the eggs and cause their release at the time of ovulation. There are worries that using gonadotropins increases the chance of conceiving multiples and having a baby too soon [26]. As gonadotropins are the same as human pituitary FSH, administering them to the body would stimulate the formation of ovarian follicles. The main method for increasing fertility is to stimulate several follicles, which results in the production of numerous eggs [27]. FSH and luteinising hormone (LH) cooperate to promote folliculogenesis and ovulation in humans. They help ovarian output by controlled ovarian stimulation (COS). The quantity of oocytes created during IVF [28]. Medication for gonadotropins is administered subcutaneously via injection (i.e. under the skin with a very small needle). A significant increase in the expression of proapoptotic cell genes in the stratum granulosum layer is produced by supplementing with highly purified human menopausal gonadotropin (HP-hMG), which contains hCG-driven LH bioactivity, according to studies. This suggests that HP-hMG may play a key role in the developmental competence of the oocyte [29]. These medications cannot be given orally since doing so would cause the digestive system to break down the protein hormones. Gonadotropins are available as pre-mixed cartridges that fit into a self-injection device or as a powder that is mixed with sterile water. Once it is verified that a specific number of mature eggs have grown in the ovarian follicles, medication must be taken every day. We are aware that the idea of self-injection might be frightening for many individuals. Nurses in fertility clinics encourage patients to inject themselves with ovulation stimulants and pharmaceutical companies also offer educational films for this matter [26]. Throughout the course of therapy, patients undergo routine ultrasound examinations to count and measure the size of egg follicles in each ovary and make sure the ovaries are receiving the right amount of stimulation. Patients receive an injection of HCG (human chorionic gonadotropin), commonly known as Ovidrel, when it is determined that the follicles have grown sufficiently and the eggs within should be mature. This hormone starts ovulation, the release of the egg, and the growth of the corpus luteum, both of which are necessary for progesterone production. Typically, ovulation happens 38 to 44 h following the HCG injection [26, 30]. According to the Centres for Disease Control, there were 32.3 twin births per 1000 live births, or 3% of all live births, a high record. Since 1980, when the rate was 18.9 per 1000 live births overall, there has been a 71% increase. According to the study, 43% of pregnancies resulted from assisted reproductive technologies, 38% from ovulation-inducing medicines, and 20% from spontaneous conception. Better predictors of multiple gestations should be developed due to concerns about the obstetrical and neonatal dangers associated with multiple pregnancy [31]. Among the viable pregnancies that arise with gonadotropin-IUI, there is a significant chance of high-order multiple birth (11.6%). The risk would not be reduced to tolerable levels by stopping cycles with increased estradiol levels (> 1200 pg/mL) or an excessive number of developing follicles (5) [32].

2.3.2 Surgical treatment

2.3.2.1 Male surgical Obstructive azoospermia (OA) is present in 20% of men who seek infertility treatment. About 40% of these individuals, or 21, have post-testicular obstruction, because the epididymis is bilaterally restricted, as well as the seminal or ejaculatory ducts. In post-ejaculate urine and semen, OA is the absence of spermatozoa and spermatogenetic cells. FSH levels, testicular size, and epididymal hypertrophy were all within normal limits in men with OA. The vas deferens can occasionally be missing due to birth defects or recent surgery. Anomalies of the ejaculatory, vassal, or epididymal ducts, prior vasectomy procedures, and OA are possible reasons [33].

- *Varicocele repair*: In up to 35% of cases, varicocele is thought to be the cause of or a contributing factor to male infertility or subfertility. The mechanisms underlying the detrimental effects of varicocele on male fertility are the subject of numerous hypotheses. Hypoxia, stasis, raised testicular temperature, an increase in spermatic vein catecholamine causing testicular underperfusion, and enhanced oxidative stress are some of the proposed mechanisms. Nevertheless, none of them adequately explains the variable impact of varicocele on male fertility and human spermatogenesis. There is considerable controversy over the link between varicocele and infertility. The incidence of this illness is undoubtedly higher among infertile males, though. Furthermore, there is a correlation between varicocele and decreased testicular size and semen characteristics, and improvements in semen quality and pregnancy rates following varicocelectomy provide compelling evidence of a cause-and-effect relationship. Notwithstanding these facts, it is still not apparent why most men with varicocele are still able to conceive and why their reproductive

status does not always become better following therapy [33].

- *Vasovasostomy*: Up to 6% of male vasectomy patients are thought to eventually seek reversal surgery (Fig. (6)). According to a review of the literature, a microscopic vasovasostomy produces better outcomes than a macroscopic or loupe-magnification procedure. After vasovasostomy, sperm return to the ejaculate occurs without the use of ART, pregnancy is achieved in 70–95% of individuals. The interval in years between a vasectomy and a vasovasostomy affects the rate of sperm recovery and conception. According to Silber, males who had five years or less with an obstruction increased the likelihood of productive intervals. Despite being statistically insignificant, the pregnancy rate appeared to decline with blockage duration while the patency rate did not seem to change obviously. The rate of pregnancy is also significantly influenced by the age of the female spouse [25].
- *Vasoepididymostomy*: Candidates for vasoepididymostomy should be patients who have epididymal blockage without any other anatomical anomalies. For the epididymal obstructive azoospermic male, microscopic vasoepididymostomy is regarded as the best option. Many methods for effective anastomosis have been documented since the invention of microsurgical tools and suture material [33]. Patency can be restored in 70–90% of people with microsurgical treatments; however, only 50% of people have their fertility returned. Individual patient characteristics and intraoperative variables affected the surgical success rate. Unilateral vasoepididymostomy has a low success rate, but bilateral surgery is expected to up the overall patency rate. In comparison to the caudal epididymis, In the caput epididymis, the epididymal tubules' luminal widths are narrower. The vasoepididymostomy site has been linked to the patency rate in various studies compared to the caudal epididymis, the caput epididymis has epididymal tubules with a smaller diameter. The caudal vasoepididymostomy has a higher patency rate than the caput. For vasoepididymostomy patients, sperm collection and cryopreservation during surgery is advised to prevent surgical and pregnancy failure. Men having vasoepididymostomy should have their sperm cryopreserved intraoperatively to increase their postoperative reproductive choices [25].
- *Sperm retrieval techniques in obstructive azoospermia (OA)*: In the case of congenital problems, surgery can frequently open blocked tubes in the genital system or create connections that never formed. The experts specialise in delicate procedures to safely and successfully restore your sperm flow if you have obstructive azoospermia. There is frequently a backup plan if surgical reconstruction is not an option. The experts are able to remove sperm from the:

  - Testis
  - Epididymis, the nearby tube where sperm develop.
  - Vas deferens, the tube that transports sperm from that location. With the patient, the experts will thoroughly go through the possibilities and assist in making a choice. If surgery is an option, there are two kinds: endoscopic surgery and microsurgery.

    - *Microsurgery*: is a time-tested method with a rich history. The specialists have specialised fellowship training, which entails studying for a further year to specialise in this treatment, to perform it. Prior to surgery general anaesthetic will used to sleep totally. The patient's scrotum is cut in a minor incision by the physician. Then carefully removes the obstruction or replaces the lost connection, then meticulously stitches up the wound using powerful magnification and specialised tools. Use microsurgery to fix issues with the vas deferens and the epididymis.
    - *Endoscopic surgery*: Uses a tiny incision and is a minimally invasive procedure. Prior to surgery
    - general anaesthesia is used to put someone to sleep entirely and local anaesthetic is added for comfort.
    - The surgeon guides themselves by viewing the surgical site through a special scope (extremely thin, flexible tube equipped with a camera, light, and magnification). The urethra is carefully threaded with the scope, preventing the need for an incision. Carefully remove the obstruction. Problems in the ejaculatory duct, the tube from which sperm escape into the urethra and combine with fluid to produce semen, are fixed with endoscopic surgery [34].
    - *Surgically removing an epididymal obstruction and retrieving sperm*: sometimes the epididymis gets clogged, which interferes with proper sperm ejaculation. If this is the root of the problem with infertility, the blockage can be removed surgically. The option of sperm extraction via surgery if:
    - Possess a blockage that prevents sperm from escaping
    - Being born missing the tube that removes sperm from a testicle (vas deferens)

- Have undergone a vasectomy or a vasectomy reversal that failed
- Both treatments are performed as outpatient procedures under local anaesthesia and last a few hours [25].

2.3.2.2 Female surgical There are various surgical techniques that can be utilised to examine reproductive issues and support fallopian tube surgery. You could require surgery to have your fallopian tubes repaired if they are scarred or clogged. Your fallopian tubes' scar tissue can be removed surgically to make it simpler for eggs to travel through. The degree of your fallopian tubes' damage will determine how successfully the procedure goes. Ectopic pregnancy, which happens when the fertilised egg implants outside the uterus, is one of the potential negative effects of tubal ligation. PCOS, fibroids, and endometriosis are the condition in which some of the womb lining begins to protrude outside the uterus. Cysts, which are fluid-filled sacs, are frequently removed or destroyed during laparoscopic surgery to treat endometriosis. Submucosal fibroids, which are tiny growths in the uterus, may also be removed using it. If ovulation medication has not been successful for PCOS patients, a quick surgical technique termed laparoscopic ovarian drilling may be utilised. This entails vaporising a portion of the ovary with heat or a laser [35].

- *Fimbrioplasty*: It is carried out to cure fimbrial phimosis, which is a partial occlusion of the fallopian tube's distal end. Although the tube is patent, sticky bands around the terminal end. Usually, the tube's longitudinal folds are still present. The peritoneal adhesive bands that encircle the fimbria are cut apart during a fimbrioplasty. Stretching the tube and releasing modest degrees of fimbrial agglutination are accomplished by gently inserting an alligator laparoscopic forceps into the tubal ostium, opening the forceps, and then removing them. Following laparoscopic fimbrioplasty, after two years of follow-up the rate of ectopic pregnancy was 23%, the rate of live births was 37%, and the rate of intrauterine pregnancy was 51%. The pregnancy and fecundity rates after laparoscopic fimbrioplasty were 40 and 4 per cent, respectively, compared to 56 and 16 per cent after salpingostomy, according to another study that found identical outcomes after either procedure. Ectopic pregnancy rates were generally around 5%. Salpingostomy results appear to be similar to those of fimbrioplasty. The latter approach produces tubules that are more normally shaped [35].
- *Terminal salpingostomy*: To treat the hydrosalpinx-related tubal blockage, a terminal salpingostomy is performed. The effectiveness of treatments to increase fertility is typically low, but it also depends on factors including ampullary dilatation, the existence of mucosal folds, the proportion of ciliated cells in the fimbrial end, and peritubal adhesions. After salpingostomy, there is a 30% average pregnancy rate and a 5% ectopic pregnancy rate. However, the likelihood of pregnancy can range from 0% in cases where the tube is rigid and thick without rugae to 80% in cases where tubal damage is absent or limited as determined by a hysterosalpingogram, salpingoscopy, or surgical inspection [36].
- *Fallopian tube surgery*: You might require surgery to treat obstructed or scarred fallopian tubes. In order to facilitate egg passage through fallopian tubes, scar tissue might be removed surgically. The degree of the fallopian tube damage will determine whether the procedure is successful. An ectopic pregnancy, in which the zygote implants outside the uterus, is one of the potential negative effects of tubal ligation [37].
- *Endometriosis*: Endometriosis is the condition in which some of the womb lining begins to protrude outside the uterus. Cysts, which are fluid-filled sacs, are frequently removed or destroyed during laparoscopic surgery to treat endometriosis. Submucosal fibroids, which are tiny growths in the uterus, may also be removed using it. If ovulation medication does not work for polycystic ovary syndrome (PCOS), a quick surgical technique called laparoscopic ovarian drilling may be utilised. In order to do this, a portion of the ovary must be destroyed using heat or a laser. When endometriosis is identified during a laparoscopy, surgical endometriosis therapy is frequently carried out. By an incision just below the navel, a lighted telescope is inserted to observe the pelvic cavity during a laparoscopy operation. The doctor may remove ovarian cysts, endometriosis nodules, and adhesions during laparoscopy. While treating recurring endometriosis with the intention of protecting future fertility, laparoscopy is frequently employed [38]. Endometriosis can occasionally be so severe that extensive surgery is necessary to remove both the endometriosis and adhesions. The excision of the complete ovarian cyst with its wall is preferable to just emptying the endometriotic cyst for relieving pain and preventing recurring cysts. After childbearing is finished, hysterectomy (removal of the uterus) along with ovarian removal can be used to effectively treat endometriosis. More than 90% of women experience complete pain relief from

endometriosis following this surgery. There may be a higher likelihood that the symptoms may return and that additional surgery would be necessary if one or both ovaries are maintained. After the ovaries are removed during a hysterectomy, hot flashes and other menopausal symptoms can be lessened if low-dose hormone treatment (oestrogens or progestins) is used [38].

2.4 Reproductive assistance

2.4.1 Artificial insemination (In vitro fertilisation, IVF)

Is the fusing together in a laboratory dish of a woman's oocyte and a man's sperm. Zygote mature in vivo and embryos give rise to pregnancy in the uterus; however, the phrase "in vitro" refers to outside of a living creature [39]. IVF may be the best option for women whose first-line reproductive treatments have failed. It was initially created for women whose fallopian tubes were not functioning due to tubal factor infertility [40–42]. The following are some typical cases of female infertility where artificial insemination may be a reasonable option:

- Endometriosis,
- Infertility brought on by ageing,
- Irregular menstrual cycle,
- Genetic disease risk,
- Unknown infertility,
- male partner enable to produce any sperm,
- Non-functional fallopian tube
- Bilateral tubal ligation of women,
- Anti-sperm antibodies,
- Females who experienced three failed attempts at conception.
- Less ovarian function (it suggests that women of reproductive age have fewer oocytes of lower quality and number) [43].

- Typical female infertility scenarios where assisted reproductive techniques (ART) may be a viable option include: IVF and intrauterine insemination (IUI) are advised in cases of male infertility, idiopathic infertility, or when there are considerable aberrant sperm parameters but some normal spermatozoa. In the majority of cases, pregnancy rates rise to between 40 and 50% following. When the sperm are dead (a positive result on the sperm viability staining or hypoosmotic swelling test), intrauterine insemination procedures should not be employed. IVF with ICSI should be utilised instead, according to abnormal functional sperm tests (such capacitation, acrosomal response, and sperm penetration assays) [44, 45].

2.4.1.1 IVF technique

- *Stimulation of the ovaries under control*: Ovarian stimulation is the first step in the IVF process. There have been a variety of protocols used, from no stimulation to varied degrees of ovarian stimulation utilising letrozole, clomiphene citrate, and exogenous gonadotropins (FSH and LH). In gonadotropin-releasing hormone (GnRH) analogues, the woman's LH surge is inhibited throughout IVF cycles, allowing the medical staff to time egg retrieval. Blood levels of E2 can detect any necessary changes to the stimulation regimen, while transvaginal ultrasonography tracks follicle development [46]. When using a natural cycle for IVF, the egg is removed before the mid-cycle LH surge or the release of LH is prevented by using a GnRH antagonist (GnRHant). The LH surge is replaced with hCG once the primary follicle reaches its mature size. The cycle-to-cycle pregnancy rate is roughly 8% since the annualised pregnancy rate is 21% after three cycles and can reach 44% in couples who suffer with male factor infertility. IVF cycles initiated voluntarily are less common because of the lower clinical pregnancy rate [47]. The vast majority of IVF treatments harvest 10–20 oocytes with ovarian stimulation. There are two primary methods: a GnRHant cycle or a prolonged luteal GnRH agonist (GnRHa) cycle. Beginning on cycle day 21 of the previous month, the extended luteal GnRHa regimen entails daily administration of 0.1 mg of GnRHa. The pituitary consequently stops secreting LH (and FSH) during ovarian stimulation, and the GnRHa is maintained until the injection of hCG. Starting on cycle day 2, gonadotropins are provided at doses ranging from 75 to 450 IU daily. Dose modifications are made in response to follicular development and estradiol levels. Three or more follicles must be at least 18 mm in size before the hCG injection is given. Gonadotropins (75 to 450 IU) must be given daily starting on cycle day 2 or 3 according to the GnRHant protocol. When the lead follicle diameter reaches 14 mm or on the sixth day of ovarian stimulation, the GnRHant is initiated to suppress the natural LH surge. 18 mm hCG is injected once three or more follicles have developed [46]. With or without gonadotropins, the bare minimum stimulation protocol uses the selective oestrogen receptor modulator (SERM) clomiphene citrate or the aromatase inhibitor letrozole. The pair will pay less or nothing when gonadotropin stimulation is minimised. The percentage of live births is slightly lower (49% vs. 63% vs. extended

GnRHa method) with the lowest stimulation regimen, but multiple pregnancies and ovarian hyperstimulation syndrome are far less prevalent [48, 49].

- *Oocyte retrieval*: 34 to 36 h after hCG treatment, mature oocytes are recovered, regardless of the stimulation regimen. Using intravenous sedation and ultrasound-guided transvaginal aspiration, oocyte retrieval is carried out. The ovaries are examined using a vaginal ultrasonography probe, and the accompanying needle guide helps the physician precisely place the needle into each follicle to aspirate the oocyte and follicular fluid [46].
- *Embryo fertilisation*: The oocytes are fertilised using either insemination or ICSI. To prepare the semen sample, the sperm are separated by density centrifugation and washed in high protein media to encourage capacitation, which is a necessary step for sperm to become fertile. An oocyte is incubated with fifty to one hundred thousand sperm for 12 to 18 h. ICSI, in which one immobilised oocyte is directly injected by sperm, may be necessary for male factor infertility. As a result, there is no requirement for the sperm to enter the zona pellucida, a glycoprotein matrix that encloses the oocyte [46].
- *Embryo transfer*: Embryos that have undergone fertilisation are implanted either during the blastocyst stage (5 days after fertilisation) or the cleavage phase (3 days after fertilisation). Since fewer embryos are required to accomplish the blastocyst stage transfer, it increases the number of live births per cycle and decreases the number of multiple gestations [50]. The disadvantage of transferring embryos at the blastocyst stage is that there may be fewer embryos available for transfer due to the loss of embryos that did not survive in culture until day 5. Embryos are transplanted into the uterus via a catheter inserted through the cervix under transabdominal ultrasound guidance. The embryos are separated from the uterine fundus by 1 to 2 cm. To ensure that each embryo was successfully implanted in the uterus and that none were left in the catheter following the transfer, the catheter is checked under a microscope. How many embryos are transferred depends on several factors, including patient preference, maternal age, embryo quality, and stage. More than two blastocysts should not be transferred into women under the age of 37, three blastocysts should not be transferred into women between the ages of 38 and 40, and four or more should not be transferred into women between the ages of 41 and 42, according to the American Society for Reproductive Medicine [46]. More cleavage stage embryos may be transferred due to the lower chance of successful implantation; however, the maximum number of embryos that may be transferred is two for women under the age of 35, three for those between the ages of 35 and 37, four for those between the ages of 38 and 40, and five or fewer for those between the ages of 41 and 42. Progesterone supplementation is started on the day of oocyte retrieval or embryo transfer in order to maximise embryo implantation and a continuous pregnancy. Cryopreserved extra healthy embryos are kept for future use [46].
- *Chances of success*: The age of the woman receiving treatment and the underlying cause of her infertility both affect the likelihood that IVF will be successful. A successful pregnancy is more likely to occur in younger women. IVF is typically not advised for women beyond the age of 42 since it is believed that the likelihood of a successful pregnancy is very low. The proportion of IVF procedures that resulted in a live birth in 2019 was:

  - Women under 35 (32%)
  - Women aged 35 to 37 (25%)
  - Women aged 38 to 39 (19%)
  - Women aged 40 to 42 (11%)
  - Women aged 43 to 44 (5%)
  - Women aged over 44 (4%) [51].

2.4.2 Donation

To assist intended parents in becoming parents, gamete and embryo donation involves using their own eggs, sperm, or embryos. The word "intended parent" refers to the people who will raise the kids. A woman (donor) donates her eggs to a different woman (receiver) so that the recipient can have a child. A male can help a person or a couple have a child by donating his sperm through the process of sperm donation. Sperm are released after ejaculation and are found in the fluid called semen. Intrauterine insemination, which involves injecting donated sperm into a woman's reproductive system, and laboratory fertilisation of mature eggs both employ donor sperm (in vitro fertilisation). Third-party reproduction refers to the use of donated sperm.

2.4.2.1 Egg donation uses in

- Couples who desire to have a biological child using the male's sperm but the woman has low quality or no eggs,
- Ladies with an intact uterus but no ovaries,
- Females who do not want to impart genetic traits to their offspring,
- Females age over 42.

2.4.2.2 Egg donation process The egg donor receives hormone injections to promote lot of eggs ovulation. In addition to the one egg that women naturally generate each month, the injections enable many eggs to mature at simultaneously. When her eggs are mature and ready to be removed, her fertility specialist plans the surgery. The egg donor is given a sedative before an ultrasound-guided needle is used to puncture each mature follicle and collect an egg. Several eggs will be fertilised in a laboratory using the recipient's partner's sperm or a chosen donor's sperm. The method in question is in vitro fertilisation (IVF). Afterwards, an embryo is implanted into the recipient's uterus (fertilised egg).

2.4.2.3 Sperm donor screening There is no foolproof way to ensure that DI will not spread infectious diseases. However, the following suggestions should significantly reduce these dangers, along with accurate information of the donor's background and the specific exclusion of those with a high risk of HIV and other STIs. Medical background: Consult the "Donor Eligibility Medical Questionnaire" list. Performing a "FDA Donor Eligibility Physical Exam" to assess physical health. Perform the laboratory test outlined under "FDA Donor Eligibility Laboratory Testing" within 7 days of semen production [52, 53].

2.4.2.4 Selection of sperm donors An assurance of excellent health and typical results from a semen analysis is given to a donor. The simplest requirements for normal semen quality can typically be employed, despite the fact that there are no globally accepted norms. B genetic analysis: The donor should undergo the requisite genetic testing, as is covered in the section of this document on genetic counselling. The donor should be of legal adult age in their state and young enough to minimise risks to the offspring associated with a high paternal age, such as autism, ideally R21 year donors [54].

2.4.2.5 Donor screening for oocytes There is no way to completely stop pathogenic viruses from spreading through donor oocytes. These dangers should be significantly reduced by the donor's history and the targeted exclusion of persons with a high risk of obtaining HIV and other STIs. Performing a "FDA Donor Eligibility Physical Exam" to assess physical health. For details on medical history and "FDA Donor Eligibility Laboratory Testing" within 30 days of or up to 7 days after acquisition laboratory testing, consult the "FDA Donor Eligibility Medical Questionnaire" list [52, 53].

2.4.2.6 Donor selection for oocytes Oocyte donors should be between the ages of 21 and 34, and they must be of legal drinking age in their state. Donors who are 34 years of age should reveal their age to the recipient during the discussion regarding cytogenetic risks and the effect of donor age on pregnancy rates. Donors must be in good health and have no past illnesses that might be inherited. Proven fertility in the donor is preferable but not required. Pelvic ultrasonography is suggested for assessing the anatomy of the pelvis, including the ovaries, and counting the number of antral follicles. To predict the response to oocyte stimulation, additional testing of serum ovarian reserve indicators is necessary. All donors should get a psychoeducational evaluation and counselling from a licenced mental health practitioner. The donor should go through the proper genetic testing [53].

2.4.2.7 Ethical considerations and potential emotional implications associated with third-party reproduction Gene relatedness is less significant than the quality of the parent–child bond, according to the general conclusion reached by children and families who benefit from gamete donation. However, for some people, finding the donor and other "donor relations" does seem to be significant. This leads to a paradox where genetic relatedness is presumed to be significant for the link to the donor and "donor siblings" but negligible for parent–child ties and child adjustment. It stands to reason that views on the relative (in)importance of genetic relatedness have evolved over time. A vital part of identification that children have a right to understand, whether for moral, psychological, or medical reasons, is the genetic link between a child born through donor conception and their donor. This relationship was formerly regarded to be "best forgotten", but it is now being highlighted as a crucial aspect of identity. The genetic link between a child and their donor is made more relevant by donor identification techniques alone. These "genetic" relationships have societal meaning, much to how people who share a donor are referred to as "half siblings". This approach has implications for both empirical research and ethical discussions in terms of how questions concerning gamete donation and information sharing are phrased. How much weight is given to the complex genetic links involved is also influenced by the rules governing donor conception [55, 56].

2.4.3 Intrauterine insemination (IUI)

For patients with ovulatory problems, unexplained infertility, cervical or male factor infertility, a handful of clinics use therapeutic intrauterine insemination (IUI) using partner spermatozoa as a first line of treatment [57]. It is a reproductive technique used by couples who have tried unsuccessfully to conceive for at least a year. With an IUI procedure, sperm is injected into a woman's uterus to aid with fertilisation (the joining of the sperm and egg). Cohen [58] is the first paper on intrauterine insemination

(IUI) which was published. Since then, sperm preparation, timing monitoring for pre-ovulatory periods, and hCG-induced ovulation (hCG) have all contributed to advancements in IUI. Additionally, IUI has been used with ovarian stimulation using clomiphene citrate (CC) or gonadotrophins. Despite not having the designation of an ART, it is regularly used, frequently as an empirical treatment, for a variety of infertile indications [59]. The purpose of IUI is to increase the quantity of sperm that enters the fallopian tubes, hence raising the possibility of conception. IUI gives the sperm a head start, giving it an advantage, but a sperm still needs to travel independently to the egg and fertilise it. Comparatively speaking to in vitro fertilisation, it is a less invasive and more affordable choice. Low sperm count or reduced sperm motility is the most frequent causes of IUI. However, any of the following conditions may also be treated with IUI, including infertility:

- Females have pelvic infections,
- Cervical mucus problems,
- Cervical scar tissue from previous surgeries that might prevent sperm from entering the uterus
- Endometriosis,
- Dysfunction of ejaculation,
- IUI is not recommended for the following patients,
- The presence of the fallopian tubes disease,
- Unknown infertility.

2.4.3.1 Procedures and insemination methods

- *Ovarian stimulation*: On cycle days three through seven, the women received either 50 or 100 mg of clomiphene citrate. Following that, they received daily doses of 1–2 ampoules (75–150 IU) of HMG. On cycle days 9 to 13, vaginal ultrasonography was used to assess the ovarian and endometrial responses. When at least one follicle had a mean diameter of.16 mm, HCG (Pregnyl; Organon or Profasi; Serono) in the dosage range of 5000–10,000 IU was administered. The standard IUI procedure was carried out 36 h following the HCG injection.
- *Semen preparation*: At the clinic, your partner's sperm is harvested. The low-quality sperm are separated from the sample of sperm by washing, which keeps only the best sperm that appear normal and are very active. If a concentrated sample of healthy sperm is used, the likelihood of conception is increased. You will be watched for ovulation symptoms (release of an egg). In order to stimulate the ovaries, increase egg production, and increase your chances of getting pregnant, doctors may also advise you to take medication. Usually, IUIs are carried out a day or two after ovulation has been detected. The sperm suspension may be placed in the Fallopian tube, uterus, peritoneum, or cervix. The method that is applied most frequently is IUI. Typically without the use of imaging guidance, a small catheter is utilised to transfer a sperm solution containing between 0.2 and 0.5 ml into the uterus. With a 4 ml inseminate with Fallopian tube sperm perfusion (FSP), the inseminate has the potential to partially or completely fill the peritoneal cavity in addition to the uterine cavity and Fallopian tubes [60]. For frozen semen, IUI is preferable to intracervical insemination (ICI) since, after six insemination cycles, it raises the likelihood of a live delivery by two (OR 1.98; 95% CI 1.02–3.86) [61]. FSP outperformed IUI in two investigations including patients with unexplained infertility. There is not enough evidence to say that FSP is any better than IUI for other indicators [62, 63].
- *Timing of insemination*: It is possible to inseminate once, several times, or not at all in the days leading up to the ovulation. The vast majority of published studies use insemination 32–36 h following hCG therapy. Given that it is widely believed that timing insemination in relation to ovulation is important for an optimum success rate, it is really surprising that so little study has been done to find the appropriate time for insemination [64]. A thorough review found no variation in pregnancy rates per couple with two inseminations compared to one [63].
- *Procedure*: A hormone called human gonadotropin hormone is administered during the process to release the eggs. With a catheter, your doctor administers the sample of semen directly into the uterus (long tube). You will be need to stay on your back for a short while after the treatment. The entire treatment takes little time and may only cause little discomfort.

2.4.3.2 Risks

- *Infection*: There is a very small chance that the surgery will result in an infection.
- *Spotting*: Sometimes a little vaginal bleeding occurs as a result of inserting the catheter in the uterus. Usually, this has no impact on a woman's odds of getting pregnant.
- *Multiple pregnancy*: IUI by itself does not put women at a higher risk of having twins, triplets, or more pregnancies. However, there is a considerable increase in the likelihood of multiple pregnancies when used in conjunction with ovulation-inducing

drugs. Premature labour and low birth weight are two risks that are higher for multiple pregnancies than for single pregnancies

2.4.3.3 Chances of success with IUI This relies on a variety of factors, including:

- Infertility causes,
- Females age,
- The quantity and calibre of the man's sperm (using fresh sperm leads to higher conception rates than using frozen sperm)
- Fertility medicines. It is best to discuss your unique possibilities of success with your fertility team because there are many various elements at play. IUI is a straightforward, low-tech process that has the potential to be less expensive than other forms of fertility therapy. Although it increases your chances of getting pregnant, IUI is not guaranteed to be successful because each person's body is unique.

2.4.3.4 Results Before performing a home pregnancy test, wait two weeks. Testing too soon could result in the following outcome:

- *False-negative*: The test result may be negative even though you are actually pregnant if pregnancy hormones have not yet reached detectable levels.
- *False-positive*: The chemical that remains in your system after taking an ovulation-inducing medication, such as HCG, may signify pregnancy even if you are not pregnant. A blood test, which is more sensitive in identifying pregnancy hormones after fertilisation, may be recommended by your doctor a couple of weeks following the findings of your at-home kit. If IUI does not work, you might try it again before trying any other reproductive treatments. The same therapy is usually given for three to six months to boost the likelihood of conception.
- *4–4 Intracytoplasmic sperm injection (ICSI):* Infertility in couples who were unable to conceive naturally with subzonal insemination of the oocytes or normal in vitro fertilisation (TVF) has recently been documented as being aided by intracytoplasmic sperm injection (ICSI) [65]. A single live sperm is injected into the core of a human egg. The majority of these infertile couples experienced severe male factor infertility, and the ejaculate's motile sperm count was occasionally insufficient for the couples to be accepted into an IVF programme.

2.4.3.5 Mechanism of ICSI IVF allows for both standard and ICSI fertilisation of an egg. In a laboratory dish, the egg is placed close to 50,000 or more swimming sperm during classical IVF. When one of the sperm enters the cytoplasm of the egg, fertilisation takes place. In the ICSI procedure, a single sperm is injected into the centre of the egg using a tiny needle called a micropipette. After fertilisation, whether via traditional IVF or ICSI, the fertilised egg (now known as an embryo) develops in a laboratory for one to five days before being implanted into the woman's uterus (womb).

- ICSI aids in overcoming issues with fertility such as:

- Regardless of the sperm's health, traditional IVF has not been able to successfully fertilise eggs,
- The sperm may experience difficulties affixing to the egg,
- Male reproductive tract blockage,
- Low sperm count to perform IVF or IUI,
- The eggs are in vitro matured,
- Eggs that had previously been frozen are used.

2.4.3.6 Procedure

- *Sperm collection*: If masturbation is not an option for sperm acquisition, they are surgically retrieved from a testis by making a small incision. When sperm cannot be expelled from the ejaculate or when there is a difficulty with sperm development, this treatment may be used. Doctors advise men who have few or no sperm in their semen (not because of a blockage) to seek genetic testing to search for issues that could harm their offspring before beginning ICSI.
- *Ovulation and egg retrieval*: To prepare for a therapy utilising your own eggs, you must receive daily shots and spend the two weeks prior to the egg collection under strict surveillance. The multiple egg production in your ovaries is stimulated by partners administering gonadotropin or follicle-stimulating hormone (FSH) injections at home. Superovulation is the term for this. Your doctor will monitor your blood oestrogen levels after the first week and use ultrasound to evaluate whether eggs are developing in the follicles. Your dosage may change during the second week in accordance with the outcomes of tests and ultrasounds. If the follicles have reached full development, an injection of human chorionic gonadotropin (hCG) is given to promote the maturity of the follicles. The developed eggs must be harvested after 34 to 36 h.
- *Sperm injection and transfer*: An egg is held in position using a glass object. One sperm is inserted into

the egg via a thin glass tube. Eggs are examined to see if they have been fertilised after being cultured in the laboratory for an entire night. The eggs that have undergone successful fertilisation or have had three to five days to continue developing are chosen after incubation. A small, flexible tube (catheter) is introduced into the cervix to deliver one or more to the uterus. Based on your age and other factors about you, your doctor will advise on the recommended number of embryos to transfer. The remaining embryos could be preserved for later use [66].

- The most often studied oocyte morphologies include the meiotic spindle, CC, ZP, PS, vacuoles or refractile entities, form, granulation, and viscosity of cytoplasm. Which of these forms is ideal for oocyte selection is a topic of continuing discussion. Based on numerous morphological investigations, it seems plausible to identify oocytes with a higher probability for growing into competent early embryos. If there are no restrictions, such as the patient's age, the quantity of harvested oocytes, or previous ART failures, the oocytes with clear or moderately granular cytoplasm, narrow PS, PB in an intact appearance, normally appearing meiotic spindles and CC, and colourless and birefringent ZP should be selected for the initial ART application. It is noteworthy that in order to assess these morphological criteria, many ART facilities are required to take part in a sizable sample of homogeneous cases. To more accurately predict the oocytes of high quality, advanced technologies like genomes, transcriptomics, proteomics, and metabolomics can be used in conjunction with morphological studies [67].
- Another frequently used method in the treatment of infertility is the selection of competent embryos, which helps to improve success rates and decrease the likelihood of multiple pregnancies. The embryos created by IVF or ICSI can be chosen based on their physical features and, in rare circumstances, preimplantation genetic testing for aneuploidy analysis if acquiring oocytes for fertilisation is not restricted. Evaluations of the early embryos using morphokinetic, metabolomic, proteomic, epigenetic, and genomic data are also being taken into consideration in order to choose the best early embryos. The morphological criterion for identifying competent oocytes might be used even when its therapeutic usefulness is less than expected when a case only produces a small number of oocytes because of poor reproductive features or regulatory limits [68].

2.4.3.7 Result ICSI is frequently successful when paired with in vitro fertilisation and eggs of high quality for men who have inadequate or no sperm in the ejaculate. ICSI, which takes sperm from the testicles, is thought to be the cause of 25–30% of pregnancies.

2.4.3.8 Risks

- The same risks for in vitro fertilisation,
- Ovarian hyperstimulation can caused by Superovulation,
- The embryos number implanted in a female uterus has a direct correlation with her risk of conceiving multiples. High-risk pregnancies include multiple births for both the mother and her foetuses.

2.4.4 Nanotechnology as a treatment of infertility

Nanotechnology has changed human infertility treatments because pregnancy rates after ART increased from 6 to 35% during the last four decades [66]. By including antioxidants, small compounds, and growth factors into the culture medium, it has been shown that bettering in vitro culture conditions can enhance gamete/embryo survival and developmental potential [68]. Traditional medication delivery and tissue engineering both use nanotechnology [69]. It provides the opportunity to create tools specifically designed to enhance in vitro growing systems. From 1 to 100 nm in size, nanomaterials are composed of rather large surfaces. Because of their large loading capacity, stability, and selective affinities, they may be a helpful method for delivering drugs into gametes and embryos [68].

2.4.4.1 Male infertility and nanotechnology The use of nanoparticles has improved sperm selection, semen sexing, and cryopreservation in a number of farm animal species [70–72]. It is critical to stress that a nanoparticle's size, surface volume, composition, shape, and surface functionalisation are all crucial elements in how effective they are when exposed to sperm [73–75]. Another method that could boost male fertility is the use of magnetic iron oxide nanoparticles [76].

- Semen quality is improved by separating damaged sperm cells from semen using a specific aptamer paired with superparamagnetic nanoparticles. Also, the removal of apoptosis and acrosome-reacted spermatozoa by conjugating magnetic nanoparticles with annexin or lectins was successful [77].

- Silver nanoparticles in pig sperm function as an antibacterial agent for semen preservation and storage, providing an alternative to using antibiotics [78].
- Sperm structure, including membrane integrity and mitochondrial activity, are positively impacted by zinc inclusion nanoparticles in the semen extender. These factors preserve ATP, which is necessary for sperm functioning, viability, acrosome reaction, and movement needed to reach and pierce the egg [79, 80].
- Cryopreserved semen's sperm quality can be improved using nanoparticle-based techniques. Cerium oxide (CeO_2), zinc oxide (ZnO), and selenium nanoparticles, for example, showed that by reducing ROS formation and membrane lipid peroxidation, they may maintain the viability and motility of spermatozoa when added to freezing solutions [70, 80]. Timing is crucial since prolonged exposure to silver nanoparticles in human sperm led to DNA damage, structural flaws, and an increase in ROS production. In addition, employing magnetic iron oxide nanoparticles may improve male fertility [66].

2.4.4.2 Female infertility and nanotechnology

- To speed up the development of embryos, Zn nanoparticles are added to in vitro maturation conditions. This increases the activity of the enzyme superoxide dismutase (SOD) in cumulus cells, reduces DNA damage, and reduces apoptosis in COC. Superoxide is converted into oxygen and hydrogen peroxide by the enzymes catalase (CAT) and SOD. Reactive oxygen species (ROS) and reactive nitrogen species levels are regulated by SOD to lessen the potential toxicity of these molecules [80].
- Inhibition of Connexin-43 (CX43) production by fullerenol nanoparticles caused the transzonal projections (TZPsfif) to retract, which hampered TZP-dependent transport and accelerated the return of meiosis in rat oocytes. These researchers also observed that CX43 and EGFR were disseminated perinuclearly in granulosa cells, illuminating how fullerenol nanoparticles can stop the resumption of oocyte meiosis [81, 82].
- As an oxidative stressor, linoleic acid decreases the proportion of bovine oocytes that reach the metaphase II stage, the frequency of fully expanded cumulus cells, and the proportion of blastocysts. It is interesting to note that adding 10 mg/ml chitosan nanoparticles to the COC maturation media fully reduced the oxidative effects of linoleic acid on the nuclear maturation of oocytes, cumulus cell proliferation, and blastocyst rate. Chitosan nanoparticle concentrations of 60 and 100 mg/ml reduced the percentage of completely expanded cumulus cells and the developmental competence of bovine oocytes, demonstrating the toxicity's dose-dependent character [83].
- The intracellular glutathione concentration and DNA integrity of cumulus cells were also increased by the addition of nanoselenium and nano-ZnO nanoparticles during the in vitro maturation of bovine COCs. Cultured cells need increased glutathione levels to handle oxidative stress properly [83, 84].
- The body's primary antioxidant, glutathione, aids in the preservation of all other antioxidants. It is a naturally occurring antioxidant that can be found in varying amounts in both male and female gametes. Its significance in preserving the biological value of germ cells has been verified, and it has also been linked to the process of fertilisation and early embryo development. The good news is that glutathione may both be recycled by the body and destroyed if conditions are right. Glutathione can reduce oxidative stress by halting the production of dangerous free radicals in the reproductive system. It performs the role of the cell's primary antioxidant. Low glutathione levels are an unmistakable sign of illness and impending death. Glutathione deficit has been associated to ovarian cancer and even early ovarian ageing. Autoimmune disorders, one of the factors that affect fertility, may be affected by glutathione. Higher levels of glutathione in a woman's follicle were linked to increased rates of fertilisation in IVF patients [85]. Egg quality is dependent on glutathione because it protects eggs from oxidative stress during folliculogenesis. In fact, studies have demonstrated that oocytes with greater intracellular glutathione levels develop stronger and healthier embryos. According to another study, women's ovaries have higher intracellular glutathione levels when they are younger [86]. Egg health, one of the cells most impacted by ageing, may benefit from glutathione's antiaging antioxidant properties, according to earlier studies Eggs are one of the cells most impacted by ageing. Glutathione production has a significant role in the protective effect of follicle-stimulating hormone on embryonic development [85].
- Cumulus cells from bovine COCs that underwent in vitro maturation in the presence of copper and ZnO nanoparticles had greater intracellular glutathione levels, which contributed to improved embryo development [83].

3 Conclusion

Between the ages of 15 and 49, one in eight females receives aid with conception. With the aid of an accurate diagnosis, effective therapy, and shared decision-making, many couples receiving treatment for infertility can achieve their fertility goals; however, success rates vary by age and diagnosis. Today, owing to technology, there are several options to help people with varied fertility issues. Your particular situation and the cause of your infertility will determine the best solutions for you. Both partners may mix different sorts of therapy at times when only one partner needs treatment. In fertility treatments, hormone and ovulation-supporting drugs are often employed, occasionally in conjunction with minor surgical operations. The term "assisted reproductive technology" (ART) can facilitate egg fertilisation and aid implantation of the fertilised egg in the uterine lining. The aforementioned makes it evident that infertility has grown to be one of the most significant issues that society faces, so we must look for cutting-edge, innovative, and affordable solutions to address this issue.

Abbreviations

PCOS	Polycystic ovarian syndrome
PID	Pelvic inflammatory disease
NSAIDs	Non-steroidal anti-inflammatory drugs
NICE	National Institute for Health and Care Excellence
BBT	Basal body temperature
LH	Luteinising hormone
EBM	Endometrial biopsy
TSH	Thyroid-stimulating hormone
FSH	Follicle-stimulating hormone
HSG	Hysterosalpingography
SHG	Sonohysterography
ART	Assisted reproductive techniques
MRI	Magnetic resonance imaging techniques
WHO	World Health Organization
hCG	Human chorionic gonadotropin
GnRH	Gonadotropin-releasing hormone
HMG	Human menopausal gonadotropin
OA	Obstructive azoospermia
IVF	In vitro fertilization
GnRH	Gonadotropin-releasing hormone
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
CC	Clomiphene citrate
ART	Assisted reproductive technology
FSP	Fallopian tube sperm perfusion
ICI	Intracervical insemination
CeO_2	Cerium oxide
ZnO	Zinc oxide

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Ethics approval and consent to participate

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Consent for publication

I agree.

Competing interests

The author declares that he has no competing interests.

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