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Male Infertility: Etiology and Evaluation

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Abstract

Infertility is defined as the unable to conceive despite having one year of regular unprotected intercourse. It affects both genders globally. The increase in incidence is also due to delaying the start of families in many couples. Infertility is generally classified into two categories when a couple is unable to conceive after at least 1 year of unprotected sexual intercourse is termed primary, while any couple who has conceived previously but is not unable to conceive again is called secondary. The couple should consider the evaluation, if either partner has any known risk factor for infertility (e.g., advanced female age, male with a history of undescended testicles), or if the couple has concerns about their fertility potential. In most cases, it is recommended that both partners be evaluated simultaneously to prevent any delays in successful treatment. According to the WHO report on reproductive health, infertility may affect 15% of couples per year globally, of these, 20% will have a male factor that is solely responsible; male factors will contribute to an additional 30% of cases. When a man has any problem with his reproductive system it can lead to male infertility. Exposure to toxic substances, chemotherapy, radiation, and physical problems with the testes. Lifestyle, notably poor health habits and conditions (smoking, obesity, excessive alcohol consumption, use of drugs, testosterone, or anabolic steroids) may cause infertility in both sexes. Undescended testicle (cryptorchidism), Past inflammation of the prostate or past genital infections and/or high fever, Injury to or Torsion (constricted blood flow to a testicle), exposure to certain medications, pesticides, and other toxins, injury to the spinal cord, prostate surgery, hormone problems, genetic or chromosomal conditions testicular cancer, vasectomy, sexually transmitted diseases, varicocele (dilated veins in the scrotum), Ejaculatory disturbances Early or late puberty, Exposure of the genitals to high temperatures, Hernia repair can cause infertility.

Keywords: Male, Infertility, Azoospermia, Oligospermia, Varicocele

Introduction

The inability to conceive a child after one year or more of unprotected sexual intercourse is called infertility, Infertility can make an impact on couples throughout the world when they are looking to have a child. It is thought that 1 out of every 6 couples deals with infertility. It affects about 15 percent of couples worldwide (1). Infertility had been traditionally thought of as a primarily female problem; urologists now realize that in about 20% of these couples, some male factor may also be a contributor to their infertility. A male factor is the sole reason in approximately 20% of infertile couples. The American Society of Reproductive Medicine (ASRM) estimates that about a third of infertility cases are due to a male partner. Another third is female (2). In the last third of infertile couples, the problem is caused by either a combination of reasons or, in 20 out of 100 cases, it can't be explained.

Male infertility

Male infertility is any condition in which the man adversely affects the chances of initiating a pregnancy with his female partner. In a broader term, problems arise when the man cannot produce or deliver fully-functioning sperm. As with women, the causes of infertility in men are varied and include a range of chronic conditions, illnesses, genetic, infectious, congenital, idiopathic, and lifestyle issues (3). The urologist can best evaluate underlying causes, which will be briefly discussed in this article.

Mechanism of fertilization under normal conditions

When everything is working, as usual, a man's body makes cells called sperm. Sperm are made in the testicles (4, 5). They are stored in the epididymis, which is the tube that connects a testicle with the vas deferens. Sperm are nourished by semen. A man's fertility depends on his ability to make enough healthy sperm that can then be delivered to the female partner. The sperm travel through her cervix into her uterus to her fallopian tubes (6, 7). There, if sperm and egg meet, fertilization happens. The whole system only works when genes, hormone levels, and environmental conditions are right. “Historically, if a couple had problems getting pregnant, the woman would get checked first and the man would get checked second," said Ajay Nangia, MD, professor of urology at the University of Kansas Health System in a podcast for the Urology Care Foundation. "As time has gone by, however, more people are aware that the man and woman should get checked at the same time if they are having trouble getting pregnant,".

Causes of male infertility

Normal male reproduction depends on two major mechanisms, healthy sperm that can fertilize the egg and an erection and ejaculate so the sperm reaches the egg. Problems with either of these may mean you have infertility (8). Some causes of male infertility can be corrected with specific surgery or medication while other causes can be identified but not

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reversed. Generally, male infertility is identified by abnormalities on a semen analysis; however, other issues can contribute to infertility despite normal semen. The causes of infertility can be divided into two groups: production problems or obstruction (9, 10).

Production problems

a. **Varicocele**

Researchers believe that the major cause of male infertility is a varicocele, an enlargement of veins inside the scrotum that drain the testicles. As many as 16 percent of all men are believed to have varicoceles, but up to 40 percent of infertile men have them. And, in secondary infertility cases—those couples that successfully conceived one child with no problems, but are unable to do so again—more than 70 percent of men are believed to have a varicocele (11-13).

Physicians are not entirely sure why these enlargements cause infertility, though they suspect that the enlarged veins cause a rise in temperature in the immediate region, leading to decreased sperm production, and damaging sperm's speed and shape. Varicocele can harm sperm growth by blocking proper blood drainage (14). It may be that varicoceles cause blood to flow back into your scrotum from your belly.

b. **Medication**

Certain medications can affect sperm production, function, and ejaculation. Such medications are usually prescribed to treat conditions like arthritis, depression, digestive problems, infections, anxiety or depression, hypertension, and even cancer (15).

c. **Hormones**

Hormones produced by the pituitary gland are responsible for stimulating the testicles to make sperm (16). Therefore, when levels are severely low, (hypogonadism) poor sperm development can result.

d. **Sperm disorders**

Problems with the production and development of healthy sperm are the most common problems of male infertility. Sperm may be underdeveloped, abnormally shaped, or unable to move properly (17). Or, normal sperm may be produced in abnormally low numbers (oligospermia) or seemingly not at all (azoospermia). This problem may be caused by many different conditions, including; Infections or inflammatory conditions. Infection with the mumps virus after puberty(18, 19). Environmental and lifestyle factors. These include tobacco use, heavy alcohol use, use of marijuana or steroids, or exposure to toxins. Sperm problems can be from traits, people are born with. Other causes of low sperm numbers include long-term sickness (such as kidney failure), childhood infections (such as mumps), and chromosome or hormone problems (such as low testosterone). About 4 out of every 10 men with a total lack of sperm (azoospermia) have an obstruction (blockage) within the tubes the sperm travel through. A birth defect or a problem can cause a blockage (20-23).

e. **Smoking**

Smoking cigarettes has been linked to impaired morphology and motility of sperm cells.

f. **Alcohol**

Alcohol may interfere with sperm development and hormone levels.

g. **Temperature**

Studies prove that direct heat, hot baths, and hot tubs are real factors that can play a role in male infertility. "Other issues like wearing boxers or briefs, or just being hot outside don't make any real difference," reports say.

Obstruction/blockage problems

Sometimes the tubes through which sperm travel can be blocked. Repeated infections, surgery (such as vasectomy), swelling, or developmental defects can cause blockage. Any part of the male reproductive tract can be blocked (24). With a blockage, sperm from the testicles can't leave the body during ejaculation. Normal sperm production takes three months, the final two and a half weeks of which are spent traveling from the testicle to the outside. The distance over which sperm must travel is 15 to 20 feet, mainly through tiny, microscopic tubules. The body produces fresh sperm every day, and the sperm supply gets replenished at least every 64 days (25). Infertility in men could be due to low or poor quality sperm production, or blockages in the urinary tract that prevent the passage of sperm.

The tubules may be blocked for the following reasons:

a. **Previous Vasectomy**

One of the most common conditions causing infertility is blockage of the vas deferens from a prior vasectomy (26). A vasectomy reversal performed by skilled microsurgeons is a highly effective means of restoring fertility. In many other cases, male infertility can be treated successfully through medical and surgical therapies.

b. **Retrograde ejaculation**

Retrograde ejaculation occurs when semen pushes back into the bladder instead of out of the penis. This is caused by the failure of nerves and muscles in the bladder and neck to close during orgasm (27, 28). It is one of several difficulties couples may have delivering sperm to the vagina during intercourse. Semen may have normal sperm, but the semen is not released from the penis, so it cannot reach the vagina. Retrograde ejaculation can be caused by previous surgery, medications, or diseases affecting the nervous system. Signs of this condition may include cloudy urine after ejaculation and diminished or "dry" ejaculation with orgasm (29-31).

c. **Inflammation**

repeated infections or scarring may block the normal passage of sperm at any portion of the male reproductive tract and cause obstruction.

Immunologic infertility

Sometimes a man's body makes antibodies that attack his sperm. Triggered by a man's immunologic response to his sperm, antibodies are usually the product of injury, surgery, or infection. In attacking the sperm, they prevent normal movement and function of the sperm. Although researchers do not yet understand just exactly how antibodies damage fertility, they know that these antibodies can make it more difficult for sperm to swim to the uterus and penetrate eggs (32). This is not a common cause of male infertility.

Genetics

Genetics play a central role in fertility, particularly since sperm carry half of the DNA mix to the partner's egg. Abnormalities in chromosomal numbers and structure as well as deletions on the important Y chromosome present in normal

males can also impact fertility. Genetic diseases, such as cystic fibrosis or hemochromatosis can contribute to this (33).

Structural problems

Anything that blocks the genital tract can stop the flow of semen. This could be a genetic or birth defect. Infection or inflammation from a sexually transmitted disease can also block semen. Other causes include scar tissue from surgery or twisted, swollen veins in the scrotum (34).

Occasionally the underlying cause of infertility or an abnormal semen analysis cannot be identified, in which case it is termed idiopathic or unexplained infertility (35). As the word suggests, these men do not have a known cause for their infertility but it is thought to likely be due to genetic defects that have not been described yet. These cases may be amenable to non-specific or empiric treatment to improve the chances of conception.

Other factors

Other factors may include erectile dysfunction or premature ejaculation. Liver or kidney disease, or treatment for seizure disorders are examples of problems that can cause infertility (36).

History and physical examination

If a man is having trouble with infertility, it is worth it for him to see a urologist as soon as possible to find out the root cause. The urologist will take a medical history and do a routine painless physical exam and gathering a semen analysis is incredibly important in the workup of the infertile male (37). For many men, these steps will be enough to pinpoint the issue. But if needed, extra tests such as an ultrasound, blood work, or a hormonal profile may be ordered to further check the potential cause. A thorough and complete history should include:

1. Male infertility risk factors such as a history of bilateral cryptorchidism, vasectomy, chemotherapy, or radiation treatments (38).
2. Female infertility risk factors, including advanced female age (over 35 years)
3. Detailed Reproductive history includes

- Duration of infertility, coital timing and frequency, and sexual health.
- Duration of infertility and prior fertility.
- Childhood illnesses and developmental history.
- Systemic medical illnesses, prior infections, and medications. (e.g., diabetes mellitus and upper respiratory diseases)(39, 40).
- Sexual history including sexually transmitted infections.
- Gonadal toxin exposure including heat and testosterone.
- Exposure to potential gonadal toxins, such as heat, radiation, chemical solvents, or pesticides.

4. Prior traumas or Surgical history (with a focus on GU and inguinal surgery)
5. A review of medications (prescription and non-prescription) as many drugs can contribute to infertility
6. Lifestyle exposures such as alcohol, marijuana, and tobacco use as well as vocational exposures
7. Family reproductive history

A thorough physical exam includes an assessment of body habitus, hair distribution, breast development, and external genitalia. Specific attention is given to the size and consistency of the testicles as well as the structures within the spermatic cords: the vasa deferentia and possible varicoceles (41-42).

As mentioned before, the physical exam is very important in the workup of a man with infertility, with particular focus on the GU (genitourinary) exam. That should include:

- Examination of the penis including the location and size of the urethral meatus.
- Palpation of the testes and measurement of their size.
- Presence and consistency of both the vas deferens and epididymides.
- Presence of a varicocele
- Secondary sex characteristics include body habitus, hair distribution, and breast development (43).

When a varicocele is palpated it is graded as follows:

- Grade 0 (subclinical): seen on ultrasound only but not physically palpable.
- Grade I: palpable when the patient is performing the Valsalva maneuver.
- Grade II: palpable without Valsalva (44).
- Grade III: able to visualize varicocele through scrotum (“bag of worms”)(45)

The diagnosis of congenital bilateral absence of the vasa deferens (CBAVD) and varicocele is established by physical examination. Scrotal exploration and imagining are not needed to make these diagnoses so make sure a good physical exam is part of the evaluation workup for any man who complains of infertility (46).

The purpose of the male infertility

Evaluation

1. Identify and correct the reversible causes of male infertility with the goal of allowing a couple to conceive through intercourse, or with the least amount of technology;
2. Identify irreversible conditions that may be amenable to treatment with assisted reproductive technology (ART) using the male partner’s sperm;
3. Identify irreversible conditions in which the man’s sperm are not obtainable, in which case the couple may consider donated sperm or adoption (47);
4. Identify medical diseases that may be associated with infertility and require treatment;
5. Identify specific genetic causes of infertility that may be transmitted to and impact offspring.

Diagnosing & treating infertility in men

The first step in diagnosing male infertility is taking a medical history and performing a physical exam. The patient normally also provides a semen sample for laboratory analysis of the quantity of seminal fluid, sperm count, sperm motility, and morphology. Often patients also undergo blood testing for the identification of any hormone issues (48).

1. Sperm count (semen analysis)

A semen analysis is the most important laboratory evaluation for a man with infertility, and in many circumstances is performed before the initial consultation. To allow for an accurate interpretation of the results, the test must be performed in a standardized fashion: 2 to 5 days of ejaculatory abstinence; no exposure to lubricants that may be toxic to sperm; and maintenance of the specimen at body temperature (or near to) with delivery to the laboratory within one hour (49). Semen analysis provides information on the volume of the ejaculate, sperm concentration and motility, and the appearance of sperm under the microscope (morphology). Reference values for semen are set forth by the World Health Organization. WHO Semen Analysis Reference Values are presented in the most current guidelines published by the WHO (World Health

Organization) on their 5 th edition. (World Health Organization, 2010) are Ejaculate volume of 1.5 – 5.0 mL, the appearance of Grey and opaque, pH> 7.2 Sperm concentration >20 million/mL, Sperm motility >50% motile, Total motile sperm count >20 million motile sperm, Morphology >40% (>32% progressive). Men may have a significant variation in their semen parameters; therefore it is important to have at least two semen analyses before any conclusions are drawn. Further, there can be laboratory variation in how semen analyses are performed so additional tests are performed to confirm results (50). These tests include the assessment of leukocytes, anti-sperm antibodies, reactive oxygen species, and sperm DNA integrity. If the ejaculate volume is low, a post-ejaculate urinalysis should be performed to evaluate for retrograde ejaculation. Even if the semen test shows low sperm numbers or no sperm, it may not mean permanently infertile. It may just show there's a problem with the growth or delivery of sperm. More testing may be needed. Even if no sperm are seen on a semen analysis, then treatment may be possible (51). A proper semen analysis takes time and very specialized training by the andrologist so ideally this test is done at a center that does a lot of them. While many routine laboratory tests have a relatively set cut-off point between normal and abnormal (white blood cell count, troponins, creatinine, etc.), semen analysis does not have this kind of differentiation despite what the "normal" lab values you will see listed net to most semen values. This is because of how the data was originally designed (52). Essentially, the original studies involved taking a bunch of men who had conceived with their partner within the last year and having them perform a semen analysis. A large bell curve distribution was noted and the authors somewhat arbitrarily decided that anything better than the 5 th percentile would be considered "normal". This means that a patient with a barely "normal" semen analysis still has worse semen parameters than 95% of fertile men. This is an important fact to consider when interpreting results and counseling patients. Despite these limitations, it is still the single best test we have when evaluating these patients.

2. Blood tests

Blood tests focus on testing for hormonal and genetic causes of infertility. The hormones produced by the hypothalamus are GnRH (gonadotropin-releasing hormone) which stimulates the pituitary gland. This in turn causes the pituitary to release FSH (follicle-stimulating hormone) and LH (luteinizing hormone). FSH acts on Sertoli cells to initiate meiosis and spermatogenesis. It also causes the Sertoli cells to release Inhibin, a molecule that causes negative feedback inhibition. LH acts on Leydig cells to stimulate the production of testosterone which also acts as a potent negative inhibitor of FSH and LH release from the pituitary (53). Estradiol is made from the conversion of testosterone by aromatase. Derangement of one or more of these hormones can lead to fertility problems.

3. Hormonal Profile

The levels of hormones are checked to learn how well the testicles make sperm. It can also rule out major health problems. For example, follicle-stimulating hormone (FSH) is the pituitary hormone that tells the testicles to make sperm. High levels may mean your pituitary gland is trying to get the testicles to make sperm, but they won't.

4. Endocrine evaluation

The testes produce male hormones (testosterone and its metabolites) and mature sperm in response to specific hormonal signals from the brain (the hypothalamus and the anterior pituitary gland). Hormonal abnormalities can contribute to poor sperm production (spermatogenesis) and may be correctable in certain circumstances (54). The endocrine tests include measurement of serum testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and occasionally estradiol (E2). Not all men require endocrine evaluation, but testing should be done when ejaculate volume is low, sperm concentration is <10 million/mL, or if there are specific symptoms or circumstances associated with endocrinopathy.

5. Genetic testing

Genetic abnormalities may cause infertility by affecting spermatogenesis or sperm transport. Certain genetic abnormalities that cause male infertility can be transmitted to and affect the health of offspring. Therefore, the results of genetic testing may not only direct the approach to therapy but can also provide information on the presence of abnormalities that may impact offspring (55). The most common known genetic factors that contribute to male infertility are: 1) Genetic testing (karyotype and Y-chromosome microdeletion) should be performed on any patient with severe oligospermia., 2) Klinefelter's Syndrome, an abnormality of chromosomal number that results in poor testicular function, and 3) cystic fibrosis gene mutations that result in congenital absence of the vas deferens (CBAVD). More advanced testing such as sperm DNA fragmentation can also be done but is outside the scope of this discussion.

6. Imaging

Scrotal ultrasound, transrectal ultrasound, brain MRIs, and CT scans are all indicated depending on the diagnosis and workup. Scrotal ultrasound is good for diagnosing testicular tumors and confirming the presence of a varicocele in obese or otherwise difficult-to-examine patients. A transrectal ultrasound can help diagnose ejaculatory duct obstruction and a brain MRI can rule out a prolactinoma as a cause of infertility if the prolactin is elevated.

- **Ultrasonography**

Ultrasound (US) is a non-invasive imaging test that utilizes high-frequency sound waves to visualize the internal structures of the body. US of the scrotum and its contents may be performed when physical exam findings are unclear.

Transrectal US (TRUS) should be performed when the ejaculate volume is low without any other explanation. The purpose of TRUS is to visualize the prostate, seminal vesicles, and ejaculatory ducts to evaluate for ejaculatory ducts are poorly formed or blocked (56).

7. Testicular biopsy

If a semen test shows a very low number of sperm or no sperm you may need a testicular biopsy. This test can be done with general or local anesthesia. A small cut is made in the scrotum. It can also be done in a clinic using, a needle through the numbed scrotal skin. In either case, a small piece of tissue from each testicle is removed and studied under a microscope (57). The biopsy serves 2 purposes. It helps find the cause of infertility and it can collect sperm for use in assisted reproduction (such as in vitro fertilization; IVF).

Conclusion

In couples that have difficulty with conception, 50 percent of the time it is due to a male factor and 50 percent of the time there is a female factor. Male infertility can be due to genetic,

developmental, or exposure factors. Urology Associates offers both evaluation and treatment for male infertility, which commonly is due to issues with sperm production. Male infertility is a common condition, and typically very treatable. Most often, the cause is related to the process of making or moving the sperm. For example, some men have sperm that have a short life span. Other men can have a very low sperm count (oligospermia). And some men cannot make sperm at all (azoospermia). Sometimes these problems can be reversed. Other times, they cannot(58). This is why it is important to early evaluate and sort it out. "It's important for men to know there are treatable and reversible causes of male-factor infertility," said Stanton Honig, MD, clinical professor of urology at Yale School of Medicine. "There are things we can adjust in terms of lifestyle, medical treatments, or surgical treatments that can make a difference." The goal of the evaluation is to identify and correct any reversible causes which can delay your journey toward parenthood (59-61).

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Ethical Approval

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Authors' contribution

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