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General Insight about Male Infertility: Review Article

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ABSTRACT

Background: Failure to get pregnant after 12 months of unprotected sexual intercourse is described as infertility. Infertility affects 15 percent of the world's population, and in 50 percent of cases, a male component, such as poor sperm quality, is involved. Male infertility is now a mystery, with many theories as to what causes it. Semen analysis abnormality is usually invariably a sign of male infertility, but other male variables may still play a role even if the semen analysis is normal. Infertility in males can be caused by varicocele, genital infections, endocrine disruptors, genetic and immunological and systemic illnesses as well as environmental causes.

Objective: To discuss overview of male infertility causes, risk factors, diagnosis with special care of semen analysis.

Methods: PubMed, Google scholar and Science direct were searched using the following keywords: Male Infertility, Semen analysis and Risk factors of infertility. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included between May 2012 and July 2021. Documents in a language apart from English have been excluded as sources for interpretation was not found. Papers apart from main scientific studies had been excluded: documents unavailable as total written text, conversation, conference abstract papers and dissertations.

Conclusion: Male infertility accounts for over 20% of all causes of infertility in couples, and semen analysis is the only test that can reliably diagnose 9 out of 10 men who have a real issue with male infertility, with a sensitivity of 89.6%.

Keywords: Male Infertility, Risk factors of infertility, Semen analysis.

INTRODUCTION

One year of unprotected intercourse can result in infertility in approximately 15% of couples. One-third to one-half of all infertile couples have a male component to blame, and another third to one-half have a contributing factor[1].

Semen analysis abnormality is usually invariably a sign of male infertility, but other male variables may still play a role even if the semen analysis is normal. Several conditions can cause male infertility. Some of these diseases, such as ductal blockage and hypogonadotropic hypogonadism, are recognized and reversible. Other disorders, such as viral orchitis-induced bilateral testicular atrophy, are detectable but not curable. Idiopathic conditions are those in which the cause of an abnormal semen analysis cannot be determined, as is the situation with many cases. It's called 'unexplained infertility' when a normal semen analysis and a partner examination don't reveal the cause of infertility. Fertility-essential sperm can be found in patients with normal semen analysis. In order to determine these conditions, the male examination is necessary[2].

Men's fertility can be improved and conception can be achieved through sexual activity if reversible problems are found and treated. It's possible that azoospermic patients may still be capable of producing their own eggs. Finding disorders that don't respond to therapy will spare couples the agony of trying unsuccessful treatments [2].

Couples can be alerted to the possibility of passing down health-related genetic defects to future generations if certain hereditary reasons of male infertility can be identified. As a result, the couple may benefit from receiving genetic counselling if they undergo an adequate male evaluation. In the absence of a specific treatment, assisted reproductive procedures such as sperm retrieval from the testicles or epididymis and intracytoplasmic sperm injection may still be an option. Adoption or therapeutic donor insemination are other options for such couples. Finally, male infertility may be a symptom of a more serious medical condition that has to be addressed. There can be grave implications if cancer of the testicles or pituitary tumors are not identified, including death in rare cases. Men who are unable to conceive naturally should have their fertility evaluated to determine whether there are any issues that may be corrected or whether there are any conditions that cannot be corrected and for which donor insemination or adoption may be a possibility. Genetic problems if assisted reproductive techniques are used, which may influence the health of the offspring if the infertility is life- or health-threatening [3].

The aim of the review of article was to discuss overview of male infertility causes, risk factors, diagnosis with special care of semen analysis.

Causes and risk factors of infertility:

estimates that 50% of male infertility cases are the result of an unknown cause. Non-genetic and genetic factors are the most common causes of male infertility. Among the non-genetic factors that affect fertility, previous exposure to disease is one of the most important. Men with diabetes are at an increased risk of sperm nuclear and mtDNA damage, which may affect their ability to become pregnant. For optimal testicular function, an ambient temperature of 2°C to 4°C below body temperature is required. For the next six months, a fever of 38°C or above can disrupt spermatogenesis [4].

Other:

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Table (1): Other causes and risk factors of infertility [4]

1-Primary hypogonadism (40-50%)	13-Epididymal absence or obstruction.
2-Aging	14-Hypogonadism secondary (1% to 2%).
Obesity	15-As a result of a tumor or external infusion of androgens).
3-Androgen sensitivity	16-Congenital hypogonadotropic hypogonadism.
4-Congenital or developmental testicular disorder	17-Estrogen excess state (e.g. tumor)
5-Medication (alkylating agent, antiandrogens, cimetidine, ketoconazole, spironolactone).	18-Infiltrative disorder (e.g. sarcoidosis, tuberculosis).
6- Orchitis including mumps orchitis	19-Prader-Willi syndrome, for example, is a multiorgan genetic illness).
7-Radiation.	20-Pituitary adenoma.
8-Systemic disorder.	21-Trauma.
9-Testicular trauma.	22-Infectious genital disease (Chlamydia, Gonorrhea, Syphilis, HIV, HPV (human papillomavirus), Trichomoniasis, Pubic lice ('crabs'), Herpes).
10-Y chromosome defect.	23-Alcohol abusing.
11-Ten to twenty percent less sperm transfer).	24-Smoking.
12-Without a vas deferens or any other impediment	

Diagnosis and evaluation [5]:

Failure to become pregnant after one year of unprotected sex is described as infertility. Find out the risk factors and possible reasons of infertility by taking a detailed history.

Asking about [5]:

1-Infertility is more common in older women than in younger ones, therefore he should consider his partner's age.

2-Pregnancies or children already had, and the length of infertility.

3-Recreational drug and alcohol use.

4-Use of androgens, whether illegal or prescribed.

5-The presence of blood or pus in the sperm or ejaculate suggests epididymitis or prostatitis. Sperm quality can be compromised or obstructive azoospermia can be caused by genitourinary infection symptoms (which may or may not be sexually transmitted).

6-Symptoms of hypogonadism (low testosterone) include a loss of sexual drive, weight gain, muscle mass loss, and abnormal breast development.

7-Symptoms that point to a tumour or varicocele in the testes.

8-A pituitary adenoma can cause symptoms such as headaches and vision problems.

9-Infertility runs in the family.

10-The hypothalamus secretes gonadotrophin-releasing hormones that help promote healthy testicular function when patients have cancer or diabetes for a long period of time. Testicular germ cells, which are essential for sperm production, may be directly harmed by chemotherapy or radiotherapy.

11-Sperm-depressing medications (infographic). Retrograde ejaculation can be caused by selective serotoninergic reuptake inhibitors. Anti-androgenic properties of spironolactone

12-Accidentally created obstructive azoospermia through orchidopexy, hernia repair, or bladder surgery.

Key elements of infertility evaluation in men [6]:

History:

1. Sexually explicit acts (includes lubricant use and the frequency with which intercourse occurs (as well as the time and frequency of intercourse)

2. Historical evolution

3. Chronic diseases like diabetes, thyroid disease and hypertension are examples of medical history. Genital disorders like orchitis and hereditary disorders are other examples of medical history.

4. Sexually transmitted disease risk, symptoms of genital infection

5. Previous fertility and the length of infertility treatment.

6. Pain and swelling (e.g. dysuria, urethral discharge).

7. Medications

8. History of surgical procedures (e.g. previous genitourinary surgery).

9. Exposure to toxicants.

Examination [6]:

1. Hernia.

2. Presence of vas deferens.

3.Genital infection (e.g. prostate tenderness, discharge).

4. Testicular mass.

5. Varicocele.

6. Symptoms of androgen deficit (e.g., decreased muscular mass, reduced face and body hair, increased body fat, tiny testes, tanner stage 5).

Specialized examinations and laboratory evaluation [7]:

1. Analyses of sperm (two or more samples).

2. In-depth sperm research (if initial evaluation of both partners unrevealing).
3. Completion of a full blood count (if infection suspected).
4. Testosterone, luteinizing hormone, and follicle-stimulating hormone (if hypogonadism suspected).
5. Tests for urinary, gonorrhea, and chlamydia bacteria were performed (if genital infection suspected).
6. Intravenous (I.V.) antibiotic therapy (if retrograde ejaculation suspected).
7. Scrotal ultrasonography.
8. Transrectal ultrasonography (if ejaculatory duct obstruction suspected).
9. Renal and liver function studies.

Others based on medical history and physical examination performed in the laboratory findings [7]:

1. In a patient with non-obstructive azoospermia, a testicular biopsy is recommended.
2. Blood and semen samples will also be tested for the existence of antisperm antibodies.
3. Antisperm antibodies will be found in blood and semen samples as well.

Semen analysis:

Most prominent of these are low concentration (Oligospermic), poor motility (Asthenospermia), and aberrant sperm morphology. Males were considered infertile if their sperm parameters were below the WHO standard threshold (Teratospermia). Other seminal markers for epididymal, prostatic, and seminal vesicle function are less clearly linked to infertility, such as semen volume. The most common reason of infertility is low sperm count, which accounts for 90% of male infertility issues, and aberrant semen characteristics have a positive correlation with sperm count. Sperm count, motility, and morphological issues come from a breakdown in the regulation mechanism, which includes pre-test, testicular, and post-test components **[8]**. This means that semen analysis, which has a sensitivity of 89%, is still the most useful and fundamental investigation for detecting 9 out of 10 men with a genuine problem of male infertility. Despite the fact that this test provides important information for the initial examination of an infertile male, it is not a fertility test. It provides no insights into the functional potential of the spermatozoon to undergo subsequent maturation processes required to achieve fertilization. To determine how well the sperm are maturing, as well as how they interact with the seminal fluid, this is a straightforward test. It offers information on both the quantity and quality of sperm produced (count and morphology) **[9]**.

Reduced lower reference limits for sperm analyses have been issued by the WHO: A study of over 1900 men whose spouses had a time-to-pregnancy of 12 months yielded the following acceptable 5th percentile parameters **(Table 2) [9].**

Table (2): Semen parameters [9]

Volume: >1.5 mL pH = >7.2 No sperm agglutination Viscosity = <2 cm after liquefaction Sperm concentration: >15 million spermatozoa/mL Total sperm number>39 million spermatozoa per ejaculate	**Morphology: 4% normal forms , using "strict" Tygerberg method** **Vitality: >58% live** **Progressive motility: >32%** **Total (progressive + nonprogressive motility): 40%** **+WBC :< 1x106/ml**

Optional investigations [10]:

- 50% motile spermatozoa with bound particles in a mixed antiglobulin response test.
- Immunobead test with less than half of the motile spermatozoa attached to the beads.
- Fructose in the ejaculate: 13 mcmol.
- The amount of zinc in the ejaculate is greater than 2.4 mcmol/ejaculate.
- An ejaculate of seminal neutral glucosidase contains about 20 milliunits.
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Table (3): Nomenclature for semen variables [10]

Normozoospermia	**Normal ejaculate**
Oligozoospermia	Less than 20x106/ml of sperm in the sample
Asthenozoospermia	Fewer than half of spermatozoa progress forward (categories a and b) or fewer than a quarter of spermatozoa progress ahead
Teratozoospermia	Normal-looking spermatozoa in less than 30% of cases
Oligoasthenoterato-zoospermia	Disturbances in any or all three (combination of only two prefixes can be used)
Azoospermia	The ejaculate had no sperm.
Aspermia	Ejaculate is not present.

Specimen requirement and procedure:

Self-masturbation near the laboratory or at home is used to collect the semen sample. There should be no more than seven days of abstinence before a semen sample can be taken, and clear instructions on how to collect the sample must be given to ensure that all of the ejaculate is captured. During submission, the laboratory must be informed if the sample is missing. In order to obtain more reliable results, it is recommended that two or three samples of male semen be collected **[11].**

A clean, wide-mouthed container that is safe for spermatozoa should be used to collect the sample. Between 20 and 37 degrees Celsius, the sperm container should be stored. Semen can be collected in condoms during sexual intercourse if the patient is unable to produce a satisfactory sample through masturbation. The viability and motility of sperm can be adversely

affected if latex condoms are used under certain circumstances [12].

As soon as the sperm is collected, it should be transported to a laboratory within one hour to avoid dehydration and temperature changes. When working with sperm samples, the laboratory must closely adhere to established safety protocols. The sample should be evaluated according to the WHO laboratory manual for the examination and processing of human semen. The laboratory should apply both internal and external quality control techniques to ensure that the semen samples are analysed accurately and reliably [12].

Computer-Aided Semen Analysis (CASA) [13]:

Sperm testing is a prerequisite for determining the cause of male infertility. According to these three factors, sperm concentration, motility, and morphology are among the most important. In reproductive clinics and laboratories, sperm parameters are manually analysed by andrologist technicians. There is a lot of intra and inter laboratory variability due to visual issues and weariness of the human operator, which makes the results subjective [13].

Automated techniques known as "Computer Assisted Semen Analysis" have been used since the 1980s to accomplish these analyses (CASA). The employment of a computer to process microscopic photographs can provide quantitative information about the object.

To date, reproducible and objective sperm parameter evaluation has been impossible due to CASA systems' inherent limitations caused by low-quality sperm microscopic video recordings and spermatozoid collisions with walls known as "blade lamellas." Digital image processing techniques such as picture enhancement, segmentation, object measurement, object categorization, etc. are used to process microscopic images. CASA systems are a current focus of research into improving sperm analysis. There have been a number of investigations into the automated detection of sperm [13].

Using the differential approach, spermatozoids may be tracked more quickly and with less complexity. One year later, had the idea to use the spermatozoid head's elliptical shape to look for images of blobs with this shape. The denoised image was converted to a binary image using simple thresholding. After a series of experiments, the threshold value is determined. Morphological operators eliminate pixels that are incorrectly categorised. The ratio of the major axis to the minor axis of the ellipse was utilised by the authors to identify authentic sperm and eliminate fake sperm from the study [14].

CONCLUSION

Male infertility accounts for over 20% of all causes of infertility in couples, and semen analysis is the only test that can reliably diagnose 9 out of 10 men who have a real issue with male infertility, with a sensitivity of 89.6%.

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REFERENCES

1. **Noblanc A, Kocer A, Drevet J (2012):** Post-testicular protection of male gametes from oxidative damage. The role of the epididymis. Med Sci., 28: 519–525.
2. **O'Flaherty C (2019):** Orchestrating the antioxidant defenses in the epididymis. Andrology, 7(5): 662–668.
3. **Carson S, Kallen A (2021):** Diagnosis and management of infertility: A review. JAMA., 326(1): 65–76.
4. **Choy J, Eisenberg M (2018):** Male infertility as a window to health. Fertility and Sterility, 110(5): 810–814.
5. **Schlegel P, Sigman M, Collura B *et al.* (2021):** Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. The Journal of Urology, 205(1): 36–43.
6. **Aljaser F, Tabassum H, Fatima S *et al.* (2021):** Effect of trace elements on the seminal oxidative status and correlation to sperm motility in infertile Saudi males. Saudi Journal of Biological Sciences, 28(8): 4455–4460.
7. **Ferlin A, Foresta C (2020):** Infertility: Practical clinical issues for routine investigation of the male partner. Journal of Clinical Medicine, 9(6): 1644-49.
8. **Agarwal A, Baskaran S, Parekh N *et al.* (2021):** Male infertility. Lancet (London, England), 397(10271): 319–333.
9. **Barbăroșie C, Agarwal A, Henkel R (2021):** Diagnostic value of advanced semen analysis in evaluation of male infertility. Andrologia., 53(2): e13625.
10. **Tamrakar S, Bastakoti R (2019):** Determinants of infertility in couples. Journal of Nepal Health Research Council, 17(1): 85–89.
11. **Cocuzza M, Alvarenga C, Pagani R (2013):** The epidemiology and etiology of azoospermia. Clinics (Sao Paulo, Brazil), 68(1): 15–26.
12. **Wu Z, Chen W, Fei Q *et al.* (2021):** Analysis of semen quality of 38 905 infertile male patients during 2008-2016 in Wenzhou, China. Asian Journal of Andrology, 23(3): 314–318.
13. **Finelli R, Leisegang K, Tumallapalli S *et al.* (2021):** The validity and reliability of computer-aided semen analyzers in performing semen analysis: a systematic review. Translational Andrology and Urology, 10(7): 3069–3079.
14. **van der Horst G (2020):** Computer Aided Sperm Analysis (CASA) in domestic animals: Current status, three D tracking and flagellar analysis. Animal Reproduction Science, 220: 106350.