Male Infertility – A Review

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A population size of about 150 million is considered by many to be one of the major problems for Bangladesh. Issues relating to the huge volume of demands and necessities for this huge number of people, the absolute and relative lacking in resources and the hardship that arises as a result of this discrepancy often dominates the discussions. And, so, birth control, contraception and family planning are talked about very frequently as important health issues. On the other end of the spectrum, there are couples who desires child but remain without one after years of marriage. Infertility is a recognized reproductive health problem worldwide with a profound impact on the psychology of the affected couples.

Following regular and frequent unprotected sexual intercourse, about 84% of couples in general population are expected to conceive within one year and about 92% should conceive within two years.1,2 When a couple fails to conceive even after two years of regular frequent coitus and there is no known reproductive pathology, the couple may be considered infertile.3-27 The exact prevalence of infertility in Bangladesh is not known. In European countries, about one in seven couples (about 14%) are affected with fertility problems.3,4,7,10,11,15-19,22,24,26,28-29 In the US, 7.4% of married women aged 15-44 years suffered from infertility problems.30 Contrary to the widespread belief that infertility is a female problem, infertility in the male partner contributes to approximately half of all cases. Even, in many studies infertility due to male factors is found to be the commonest single diagnostic category.31-36

Causes of Infertility in Male

Male infertility may result from various causes. In most cases, infertility is related to abnormal semen parameters in male. Once upon a time, sperm abnormalities were largely considered as idiopathic, but with advancing of knowledge and technology, explanation is being provided by changes at the genetic level. Apart from seminal causes, varicocele and male accessory gland infections were considered common causes. Systemic causes, medications and endocrinopathies were found responsible in a very low percent of cases.37 Many environmental and genetic factors have been associated with male infertility or abnormal semen production in male.

Childhood illnesses or conditions may contribute to infertility in the later life. Bilateral cryptorchidism causes significant reduction in spermatogenesis and unilateral cases usually have effects to a lesser degree. Improved fertility rate as a result of orchiopexy at early age is not established. If not corrected by puberty, undescended testis do not function and repair at a later age does not improve fertility rate.38-39 Testicular trauma and Torsion of testis both may result in atrophic testis. About 30-40% men, who had at least an episode of testicular torsion, have abnormal semen parameters.40-47 Up to 11% men with a history of testicular torsion have anti sperm antibodies present during or after the event.48-49 Early childhood mumps usually does not affect testis. But, 30% of male patients of mumps aged above 11-12 years develop unilateral orchitis and, in peripubertal and adult males, bilateral orchitis occurs in about 10% of mumps cases.50 Severe testicular damage can result from both unilateral and bilateral orchitis from mumps.

Excessive alcohol consumption can be harmful to sperm quality but alcohol consumption of up to three to four units in a day has no proven adverse effect on male fertility.51-55 Smoking is associated with reduced semen parameters in male.56-61 But relationship between male smoking pattern and male fertility is not certain. Men with BMI of more than 29 may have reduced fertility. Total number of normal-motile sperm cells may decrease with increased BMI.62 Sperm DNA fragmentation is higher in male with BMI greater than 25.63 Obesity may have a negative effect on erectile function in males with coexisting heart disease, diabetes and other existing vascular risk factors.64 Increased scrotal temperature has a close association with reduced sperm quality in healthy population.65-67

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Occupational heat exposure, sedentary work position, which may lead to increased scrotal temperature, have both been associated with abnormal semen quality. The effect of wearing tight-fitting and loose-fitting underwear on male infertility is uncertain, though there are suggestions that wearing tight-fitting ones may affect fertility adversely.

At workplaces, the number of identified chemical and physical agents is about 104,000. Due to the fast pace of their introduction, the effects on reproduction of about 95% of them on reproductive health is not known. Exposure to heat in welders, bakers and drivers lead to abnormal semen parameter. X-ray exposure causes azoospermia and reduced sperm count in radiotherapists but the effects may be reversible.

Engine drivers, diggers may suffer from oligozoospermia, asthenozoospermia due to effects of vibration. Exposure to Dibromochloropropane in pesticides causes oligozoospermia and azoospermia, which is reversible in most cases, in agricultural workers. and is also associated with reduced fertilization rate. Exposure to lead, cadmium, manganese in male metal workers, smelters, battery factory workers may cause reduced fertility through mainly affecting female partners. No association with reproductive problems has also been demonstrated in different study.

Glycol ether (solvents) has been associated with reduced fecundability and oligospermia in painters. Ethylene dibromide (pesticide), Polychlorinated biphenyl (in agricultural workers), acetone, carbon disulphide (in chemists and laboratory workers) may cause abnormal semen parameters. There is no association with reproductive problems was reported with the use of carbaryl (pesticides), Mercury (dental amalgam), Toluene, styrene (solvents in plastic and printing industry) and anaesthetic gases (in dentists and anaesthetists). This list is not exhaustive. There are many agents, for which the association is only suspected and need further evaluation.

Prescribed medications including cimetidine, sulfasalazine, long term use of some antibiotics and andogen injection can alter semen quality and cause oligozoospermia. After 3 months from withdrawal of the responsible drugs, the effect on semen quality and sperm count may be reversed. Use of α-blockers and psychotropic drugs may lead to impotence. Among recreational drugs, anabolic steroids and cocaine can have adverse effect on the semen quality.

Genetic and chromosomal alteration, after all, has its role to play in human azoospermia. Microdeletions on the long arm of the Y chromosome was detected in patients with azoospermia and this region on the Y chromosome was named azoospermia factor (AZF) region. Later, close relationship was found between this region and human azoospermia. Microdeletions were found to be concentrated in three regions according to testicular tissue type and AZF region was divided into three subregions AZFa, AZFb and AZFc. The first azoospermia culprit gene to be identified was deleted-in-azospermia (DAZ) gene, isolated in 1995 and is localized to AZFc region. Two years later, a second culprit gene, the RNA-binding motif gene (RBMY, Y chromosome), located in the AZFb region, was reported. In 1999, a new human spermatogenesis gene, USP9Y (DFR1) was identified in the AZFa region. These three genes are typical spermatogenetic genes located in Y chromosome. Culprit genes were also identified in autosomes following research based on findings in knockout mice. Heterozygous mutation in the human SYCP3 gene, located on chromosome 12 may cause early meiotic arrest. The loss of germ cells leads to clear decrease in the diameter of the seminiferous tubules and vacuole formation in the testes. Homozygous mutation of the Human aurora kinase C (AURKC) gene yields large headed polyplodiy spermatozoa and causes male infertility in human. Homozygous mutation of SPATA16 (Spermatogenesis-associated 16, also known as NYD-SP1) was found in three brothers of an Ashkenazi Jewish family having Globozoospermia, a rare (incidence <0.1% in male infertile patients) but severe teratozoospermia, characterized by ejaculates consisting completely of round headed spermatozoa that lacks acrosomes. Susceptibility to some forms of male infertility may be increased by genetic polymorphism. Polymorphism of several genes have been associated with the human azoospermic population. Polymorphism of MEI1, PRDM9(MEISETZ), SPATA17, PARP-2 and URB-2 genes are considered genetic risk factors as they may contribute to meiotic arrest leading to azoospermia. On the other hand, association has been demonstrated between polymorphisms of SEPTIN12 gene and patients with sertoli cell-only syndrome. The list is not exhaustive. There are many agents, for which the association is only suspected and need further evaluation.

History Taking in Male Infertility:
A thorough history is the first step in the assessment of suspected male infertility that should carefully include the patients’ reproductive and sexual history, developmental history, past medical and surgical history, occupational history, medication and drug history and any history of exposure to toxins or chemicals.

Any prior conceptions with the present of past partners,
previous use of conceptions, frequency and timing of coitus with current partner, frequency of masturbation and timing of first intercourse and masturbation should be included in reproductive and sexual history. Besides, any prior difficulty in achieving conception and previous evaluation and treatments received should be noted. Information about erectile and ejaculatory function should also be recorded.

Presence of unilateral or bilateral undescended testis in the childhood, the age of surgical correction, previous history of testicular trauma and testicular torsion, mumps at any age should be included in the developmental history. The timing of pubertal development, including development of secondary sexual characteristics should be recorded. Any significant delay or incompleteness in pubertal development should be noted and may be an important clue for underlying endocrinopathy.

Any co-existing systemic disease should be noted, including diabetes, liver or renal disease. History of urinary tract infection and sexually transmitted infections should also be obtained.

History of any pelvic or retroperitoneal surgery is important and should be obtained in detail. Testicular cancer and chemotherapy for it and chemotherapy for any malignancy, especially leukemia, lymphoma and sarcomas can cause alteration in male fertility and should be included in the history.

A detailed history of medications and drugs should be obtained including any use of exogenous androgens. History of alcohol consumption and dependency and smoking history may be relevant. Current and past occupations, exposure to excessive heat, radiation, electromagnetic wave or any toxin or chemicals on course of occupational undertakings, involvement of long shift works in work, level of psychological stress related to occupation should be explored during the history taking process.

**Physical Examination in Male Infertility:**

Physical examination might start with assessing penile curvature, angulation and the location of urethral opening. Careful palpation of the scrotum with the patient in standing position in a warm room should follow. The size and consistency of the testicles may be important and should be noted. An orchidometer can be used for measuring the size of testis. Examination of epididymis should include careful palpation for the caput, corpus and cauda. Full or indurated feeling of the epididymis should also be noted as fullness may indicate obstruction. Presence or absence of vas deferens can be confirmed by palpating the spermatic cord. Any vasal atrophy or nodularity, presence of varicocele within the spermatic cord and surrounding the testicles can be found. If present, varicocele can be graded by palpation and asking the patient to perform valsalva maneuver.

Secondary sexual characters can be assessed and presence or absence of gynaecomastia should be observed. Abnormal androgenization may result from underlying endocrinopathies. Excessive oestrogen, an improper oestrogen-to-androgen ratio or elevated prolactin levels can cause gynaecomastia.

Vital signs recording, BMI estimation, Thyroid gland examination, Abdominal examination for mass, organomegaly, undescended testis or ascitis are parts of routine physical examination. A per-rectal examination can be done to assess perineal sensation, rectal sphincter tone and the size of the prostate gland.127-128

**Investigations in Male Infertility:**

The investigation of a male partner in an infertile or subfertile couple starts with semen analysis. The result of semen analysis indicates fertility status of the male. Semen is collected following 2-7 days’ sexual abstinence in a clean container and the container should be transported to laboratory at room temperature. WHO has its own guideline regarding semen parameters based on semen characteristics of “recent fathers”. 5th centile is considered the lower range of reference limit. Semen parameters below this reference limit is not enough to consider a man infertile or subfertile and parameters above this level does not necessarily confirms fertility of a man, as fertility of a couple may depend on many other factors. For the diagnosis of below par semen quality, two samples should be tested three months apart at the same laboratory.128

**Table I**

<p>| Lower reference limits for semen parameters |</p>
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lower Reference Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen Volume (mL)</td>
<td>1.5</td>
</tr>
<tr>
<td>Total sperm number ($10^6$ per ejaculate)</td>
<td>39</td>
</tr>
<tr>
<td>Sperm concentration ($10^6$ / mL)</td>
<td>15</td>
</tr>
<tr>
<td>Total motility(%)</td>
<td>40</td>
</tr>
<tr>
<td>Progressive motility(%)</td>
<td>32</td>
</tr>
<tr>
<td>Sperm vitality (%)</td>
<td>58</td>
</tr>
<tr>
<td>Sperm morphology (Normal forms, %)</td>
<td>4</td>
</tr>
<tr>
<td>pH</td>
<td>&gt;7.2</td>
</tr>
<tr>
<td>Peroxidase-positive leucocytes</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Seminal Zinc (µmol/ejaculate)</td>
<td>&gt;2.4</td>
</tr>
<tr>
<td>Seminal Fructose (µmol/ejaculate)</td>
<td>&gt;13</td>
</tr>
<tr>
<td>Seminal neutral glucosidase (mU/ejaculate)</td>
<td>&gt;20</td>
</tr>
<tr>
<td>MAR test (motile spermatozoa with bound particles, %)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Immunobead test (motile spermatozoa with bound beads, %)</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
Endocrine studies in male infertility should include serum levels of prolactin, LH, FSH, testosterone and E2 (oestradiol). Antisperm antibodies can be found

**Reaching a diagnosis:**
Azospermia can be classified as obstructive or nonobstructive. In obstructive azospermia, there is adequate production of sperm but there is failure of delivery of the sperms into the ejaculate due to ductal obstruction. In the nonobstructive azospermia, there is no obstruction, rather a lack of sperm production is responsible.

Small testis with low FSH and testosterone levels suggests hypogonadotropic hypogonadism and the patient’s LH and prolactin level should be measured. Low gonadotrophin associated with elevated prolactin level is found in pituitary prolactinoma and if this is the case, MRI of Brain is necessary.

On the other hand, small atrophic testis with elevated FSH levels suggests germ cell failure. FSH level more than the typical low normal level is suspicious of defective spermatogenesis. FSH level can be raised in unilateral testicular disease. Instead of testicular biopsy, agenetic testing including a karyotype and a Y-chromosome microdeletion analysis should be offered to those with a primary testicular defect without any hormonal deficiency.

Normal-sized testis with a normal FSH level and azospermia raises the possibility of obstruction. A testicular biopsy helps to differentiate between obstruction and maturation arrest.

Low-volume azospermic semen can be found in Hypogonadism (low testosterone level), ejaculatory duct obstruction and absence or hypofunction of seminal vesicles. In Congenital Bilateral Absence of Vas Deferens (CBAVD) and complete bilateral ejaculatory duct obstruction, low-volume azospermic acidic semen is produced.

Oligoasthenoazoospermia (OAT) is the term for defects in number, motility and morphology of sperm in semen. Varicocele is the most common cause followed by environmental toxins, drugs or medications and cryptorchidism. Varicocele can be diagnosed from physical examination and sonographic study.

Defect in sperm morphology is termed teratozoospermia. Mostly idiopathic, varicoceles and effects of temperature in spermatogenesis are potential causes.

Asthenospermia refers to defect in sperm movement with only a low percentage of sperm having any motility. Antisperm antibody and varicocele may be responsible for this defect. Sperm concentration less than $10 \times 10^6$ sperm/mL should warrant estimation of serum FSH and testosterone level.

Karyotype and Y chromosome microdeletion analysis should be added to the investigation lists if the concentration is less than $5 \times 10^6$ sperm/mL. Varicocele is a common cause of low sperm density but other defects in other sperm parameters usually coexists.

No fluid production in male orgasm is termed complete ejaculatory failure (aspermia). It occurs due to retrograde ejaculation and causes include neurologic abnormalities such as spinal cord injury, diabetes mellitus, multiple sclerosis and the use of α-blockers. Impaired ejaculation can also result from retroperitoneal surgeries, including pelvic surgery and retroperitoneal lymph node dissection. Psychological disturbances and/or serotonin reuptake inhibitors may cause complete inability to obtain orgasm. Differentiation has to be made whether the case is one of true ejaculatory failure or inability to achieve orgasm.¹²⁷

Male infertility can be the consequence of many causes. Structural defect, environmental factors, genetic constitution, chromosomal abnormalities, psychological factors – any one or more of them can act alone or in combination to render a man incapable to procreate.

Abnormal anatomy of male reproductive tract can lead to the failure of delivery of sperm into the ejaculate despite adequate and normal semen production.

**Management of male infertility:**
As part of management of infertility, couple should be seen together as decisions regarding investigations and treatment affects both partners. The couple should be provided with evidence-based information regarding their care and treatment for making informed decisions. Their choice should be included strongly in the decision-making process. Written information or information through audio-visual media should supplement verbal information.

The couple should be informed about the adverse effect of stress on their relationship which might cause decreased libido and frequency of intercourse and lead to fertility problems. They might be advised to contact a fertility support group and counseling from a person not involved with the management of the fertility issues. Irrespective of outcome, Counselling may be done before, during and after every step in investigation and treatment. Fertility problems should be managed in a specialist settings with access to wider skills rather than a general hospital.

Gonadotrophin drugs should be offered to men with hypogonadotropic hypogonadism as it may improve infertility. Anti-oestrogens, gonadotrophins, bromocriptins, androgens, kinin-enhancing drugs have not been shown to
be effective in men with idiopathic semen abnormalities. Unless there is an identified infection, men with increased leucocyte count in semen should not be prescribed antibiotics as it does not improve outcome. The significance of antisperm antibody is unclear and corticosteroid has an uncertain beneficial effect.

Surgical correction of epididymal blockage may be offered in obstructive azoospermia. Patency of the duct is likely to be restored and fertility may be improved. This may be used as an alternative to in-vitro fertilization or sperm extraction. Surgical correction of Varicocele does not improve fertility rates.

Anejaculation can be managed with alpha-agonists or parasympathomimetics and neostigmine and for retrograde ejaculation alpha-agonists or anticholinergic drugs and antihistamins are used to increase sympathetic tone of the bladder or to reduce parasympathetic activity. In anejaculation, Ejaculation can be stimulated through penile electrovibration or transrectal electroejaculation by initiating spinal cord reflex activity and stimulating nerves responsible for ejaculation respectively. In case of retrograde ejaculation, sperm can be retrieved from urine. Obtained sperms can be used for fertilization through Intrauterine Insemination (IUI), In Vitro Fertilization (IVF), Intracytoplasmic Sperm Injection (ICSI) or Gamete Intrafallopian Transfer (GIFT) in the female partner. If ejaculation failure is due to anxiety or psychological problems, anxiolytics may be useful.

If the male partner has obstructive or nonobstructive azoospermia, spermatozoa can be retrieved from both the testis and epididymis using various techniques. This procedure is also useful in case of ejaculatory failure or if only non-motile spermatozoa are present in the ejaculate. Sperm is retrieved from testis or epididymis by percutaneous epididymal sperm aspiration (PESA), Testicular Sperm Aspiration (TESA) / Testicular Fine Needle Aspiration (TEFA), Testicular Sperm Extraction (TESE) from a testicular biopsy or Microsurgical Epididymal Sperm Aspiration (MESA).

In obstructive azoospermia sperm can be obtained from epididymis by PESA or MESA or from testis by TESA or TESE. Sperm can also be obtained by percutaneous puncture from naturally occurring spermatocele. In nonobstructive azoospermia sperm has to be obtained from testis by TESA or TESE and chance of sperm extraction is reduced. As the extracted sperm are immature, they have low fertilizing capacity with standard IVF and ICSI has to be used. With ICSI, it is possible to achieve fertilization with a single sperm. ICSI is also useful in men with very low semen quality. But before going for ICSI in patients with nonobstructive azoospermia or very low quality semen, consideration should be given to any underlying genetic abnormality. If a specific genetic condition is known or suspected, the couple should be subjected to appropriate counseling and treatment. Karyotype of the man should be established. Testing for Y chromosome microdeletion may be avoided as a routine procedure but the possible association of this gene with infertility should be informed to the couple.

Prior to the availability of ICSI, donor insemination was the option to solve the male infertility problem in obstructive and nonobstructive azoospermia. Donor insemination is also an option when the male partner is likely to pass on some inherited genetic disorder or infections like HIV to the fetus or when severe Rhesus incompatibility can be a problem.

Often couple may decide to avoid ICSI due to its invasive nature or due to the genetic risks involved. Many couple might find the cost of ICSI-IVF too high to afford. For them, donor insemination is the method of choice. Again, some couple may choose donor insemination as an alternative method following failure with ICSI. On the other hand, often ICSI is preferred over donor insemination on the ground that if successful, the offspring is genetically related to both parents. So a couple should be informed of the relative merits of both options and counseling should be done about the physical and psychological issues of the couple and their offspring, should they consider donor insemination.

**Conclusion:**
Infertility poses a multidimensional problem for any couple. Though predominantly it is a physical issue, the effect on psychology of both partners is enormous. From detection and in every step of evaluation and management, both partners are subjected to tremendous anxiety. Psychological stress leads to decreased morale, maladjustment between couples and may also cause decrease work performance. Social stigma is also big issues in developing country like ours. Traditionally, women are inappropriately blamed for infertility problems, where actually men are responsible almost equally. More research is needed regarding male partners’ fertility problems, especially regarding the associations with different occupations and occupational and accidental exposure to toxins, chemicals and environmental agents. As newer techniques have been developed, the opportunity for the infertile couples is more to achieve conception. Yet, many of these techniques are costly and remain beyond the affordability of a major portion of the population.

**Conflict of Interest:** None
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