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Microbial Infections and Male Infertility

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<http://dx.doi.org/10.5772/62895>

Abstract

Microbial infections can happen on a daily basis. There are specific microbial infections that are associated with the reproductive health. Infertility is a devastating health problem. It is estimated that out of 15% of infertility worldwide, around 50% is due to male partner. Infections due to *Chlamydia trachomatis*, *Mycoplasma genitalium*, hepatitis B virus, tuberculosis, *Streptococcus faecalis*, and mumps are found to be associated with male infertility. Although most of the life-threatening microbial infections have dramatically declined since the introduction of the childhood vaccination program, there are concerns about few outbreaks and the associated risk of male infertility. This chapter deals with few microbial infections, their association with male infertility, prevention, symptoms, diagnosis, treatment, and control measures.

Keywords: Microbial infections, male infertility, genital infections, *Streptococcus faecalis*, *Chlamydia trachomatis*, *Mycoplasma genitalium*

1. Introduction

With enormous growth of population, India ranks second in world with 1.28 billion. Rather population growth is a major concern, yet infertility is a devastating health problem. According to World Health Organisation (WHO), infertility is the inability of the female partner to attain pregnancy after 1 year or more of the unprotected sex. Infertility affects about 15% of the couple of which half of the reproductive problems are associated with the male counterpart [1]. Many factors, including genetic causes, intoxication, microbial infections in genital tract, changes in lifestyle, stress, and the recent trend of late marriages, contribute to this occurrence. Table 1 highlights infertility due to male genital infections. Despite enormous progress in the understanding of human reproductive physiology, the underlying cause of male infertility remains undefined in about 50% of cases, which are referred to as idiopathic infertility [2, 3].

STD: *Chlamydia trachomatis* and *Mycoplasma genitalium*

Urinary tract: *Streptococcus faecalis*

Orchitis: Small pox, mumps, measles, and tuberculosis

Damaging spermatozoa: Hepatitis B viral infection

Table 1. Male genital tract infections that may cause infertility

2. Rationale

Globally, 5.0–7.0% of the general male population was affected by infertility and the trend may increase in the future, considering the apparent decline of sperm count in industrialized countries [4]. Male infertility, a multifactorial complex disease, has been a source of concern in India lately. Recent statistics reports that the percentage of male infertility has elevated to 60% now against 40% in 1980s (New Indian express, 2015). The magnitude of the problem calls for urgent action, particularly when the infertility is avoidable in the majority of cases.

3. Causes of male infertility

Primary (when no pregnancy has ever occurred) and secondary (there has been a pregnancy, regardless of the outcome) infertility are the two forms of infertility. The former is found in 67–71% and latter in 29–33% of patients, respectively. Approximately 50% of the infertility is due to male of which 30% is due to male factors and 20% with both male and female factors. However, in approximately 30% of cases, the origins of reduced male infertility are unknown called as idiopathic. Male infertility has been associated with several genetic and nongenetic conditions.

3.1. Molecular genetics of male infertility

Genetic abnormalities, such as numerical and structural chromosomal abnormalities, were identified in men with unexplained oligozoospermia and azoospermia [5]. Chromosomal disorders, mitochondrial DNA (mtDNA) mutations, monogenic disorders, and multifactorial disorders are the genetic factors involved in male infertility.

3.1.1. Chromosomal disarrays

Renowned chromosomal abnormalities, such as Klinefelter syndrome (XXY) and specific translocations are well-documented causes of male infertility [6]. Point mutations in the androgen receptor and the cystic fibrosis transmembrane conductance regulator (CFTR) gene commonly associated with congenital vas deferens abnormalities are the two important gene defects conclusively associated with spermatogenic failure.[7]

3.1.1.1. *Y chromosome microdeletion*

Microdeletion of the long arm of the Y chromosome (Yq) is one of the prominent causes of male infertility. It was shown by 13% of azoospermic men, 1–7% of severely oligozoospermia men, and 5% of men with severe primary testicular failure and with a sperm density of less than 5 million/mL [6]. Recombination events between long stretches of highly repetitive DNA sequences during meiosis or early preimplantation development cause de novo deletions of Yq [8]. Intracytoplasmic sperm injection (ICSI), an artificial reproduction technique, may allow for the transmission of Y chromosome microdeletions to the next generation [9].

3.1.1.2. *Mutations in Mitochondrial DNA*

Mitochondria have their own genome, capable of producing many essential components of the respiratory chain, which in turn have a profound blow on sperm motility. Environmental and genetic factors may affect the quality and quantity of sperm production. Adenosine triphosphate (ATP) production by sperm mitochondria is essential because of the high demand of energy for these cells [10].

3.1.1.3. *Monogenic disorders*

Monogenic genetic disorders are an inherited disease controlled by a single pair of genes. Such disorders are inherited in a simple pattern according to Mendel's laws. Male infertility is associated with 50 monogenic disorders.

3.1.1.4. *Complex or multifactorial disorders*

Complex or multifactorial disorders result from mutations in multiple genes, often together with environmental causes. A mutation (C677T) in the gene, methylenetetrahydrofolate reductase (MTHFR), is known to increase susceptibility to various multifactorial disorders [11].

3.2. **Nonheritable causes of male infertility**

Nonheritable causes include **genital infections**, hypogonadotropic hypogonadism, testicular maldescence, structural abnormalities of the male genital tract (obstruction of spermatic ducts, agglutination of sperm), impotency, previous scrotal or inguinal surgery, varicoceles, chronic illness, medication, exposure to chemicals, environmental factors, and immunological causes.

3.2.1. *Hormonal causes*

Fertility is questioned when endocrine system is affected on exposure to certain environmental compounds. Elevated concentrations of luteinizing hormone (LH) and follicle-stimulating hormone and low concentrations of gonadal steroids cause gonadal failure, a reason for infertility. In the male, elevated concentrations of LH can result from hypergonadotropic hypogonadism (HH), which could be due to various reasons, such as primary testicular failure, seminiferous tubule dysgenesis (Klinefelter syndrome), Sertoli cell failure, and anorchia [12].

3.2.2. Hypogonadotrophic hypogonadism

Patients with this condition show decreased levels of gonadotrophins.

3.2.3. Erectile dysfunction

Of all males are affected by impotence or erectile dysfunction and can be emotionally and psychologically disabling for men and their partners; 80% of erectile dysfunction cases may be due to physical factors, such as drugs, blood flow abnormalities, nerve impulse abnormalities, and hormonal abnormalities. Remaining cases may be due to psychological factors and may be attributed to stress, performance anxiety, or misinformation about sexuality.

3.2.4. Previous scrotal or inguinal surgery

Gonorrhoea and chlamydia cause acute inflammation of the scrotal contents (usually unilateral) in young men. Painless swellings in the scrotum are common. Most of these are small, round, epididymal cysts, or spermatoceles, and no investigation or treatment is required [13]

3.2.5. Varicocele

Varicocele, a condition of palpably distended veins of the pampiniform plexus of the spermatic cord, is the most common identifiable cause of male subfertility [14]. Varicoceles feel like a bag of worms in the scrotum and can be associated with infertility [13]. "Subclinical varicocele" refers to a lesion too small to be detected by physical examination.

3.2.6. Exposure to chemicals

Various chemicals have been implicated as reproductive toxicants. Air pollutants are present in the blood, urine, and semen of exposed men and may affect sperm quality [15]. Sperm function tests have shown that high lead levels in semen samples reduce the ability of the sperm to bind to the egg and also to penetrate and fertilize the egg.

3.2.7. Environmental factors

Decreasing human sperm concentrations worldwide is alarming fact. Sperm morphology is affected by occupational heat exposure, which is a significant risk factor for male infertility, resulting in delayed conception. The male reproductive system is particularly vulnerable to the effects of the chemical and physical environment. This may be due to dramatic events or to endemic conditions of the environment, which involves industrial and agricultural pollution. Idiopathic male infertility may be due to exposure to environmental toxicants that alter the reproductive hormones, spermatogenesis, or sperm function. Semen quality has been shown to be altered on exposure to environmental ozone [16]. Environmental reproductive hazard studies report that sperm counts have declined in certain industrialized countries.

3.2.8. Immunological factors

Because immunological factors operate at almost every step in the human reproductive process, antibodies-induced damage to gametes is a major cause of immunological infertility.

Lifestyle and environmental factors [17], including smoking, can affect gamete, leading to subfertility/infertility

3.2.9. Genital infections

Acute and chronic genital tract infections are well-known causes of infertility in men. Most diseases of the reproductive system are sexually transmitted diseases (STDs), which lead to deterioration of spermatogenesis, impairment of sperm function, and/or obstruction of the seminal tract. Genital tract infections and antisperm antibody formation in men can lead to immune-mediated infertility in women [18, 19]. A strong association between inflammation of the male reproductive system and infertility has been reported [20, 21].

3.3. Sexually transmitted infection by *Chlamydia trachomatis* and *Mycoplasma genitalium*

3.3.1. *Chlamydia trachomatis*

It is well studied that chronic prostatitis (CP) due to *C. trachomatis* (CT) infection has a significant impact on a couple's reproductive health [22]. Tissue culture was an early method for the diagnosis of CT infection. In this method, bacterium was inoculated with specimen, such as urine, grown on cell monolayers. However, cell culture was too insensitive for noninvasive samples, such as urine and semen that were also found to be toxic to the growth and maintenance of the monolayer [23]. Molecular methods, such as in situ hybridization (ISH) and nucleic acid amplification testing (NAAT), were early methods used. NAATs were more effective in detecting asymptomatic chlamydial infection on noninvasive samples, such as urine. ISH was superseded once the NAAT become widely available. In-house, polymerase chain reaction (PCR) is the first test used to detect *C. trachomatis* in clinical samples during the development of NAAT. NAAT is more reliable because of its high sensitivity, whereas ample variation in the results was observed with in-house PCR [26]. Molecular methods, such as ligase chain reaction (LCR) and PCR, showed better sensitivities than nonmolecular methods, such as enzyme immunoassay (EIA) test or direct immunofluorescence (DIF), for detection of *C. trachomatis* antigen [25].

Alternatively, sperm can also be used as a sample for all molecular methods. In case of NAAT, an important issue to be considered in selecting semen as a test specimen is there are more NAAT inhibitors [25]. Another difficulty in using sperm as a sample is that during ejaculation, semen may become contaminated with elementary bodies in the urethra, and also the organism has the ability to adhere to sperm and is not always removed from sperm by density centrifugation prior to intrauterine insemination (IUI) or in vitro fertilization (IVF)/ICSI [25].

3.3.2. CT and male infertility

C. trachomatis can cause urethritis, epididymitis, and orchitis in men, and it is also found to affect sperm by decreasing sperm motility, deteriorating sperm morphology and viability and increasing proportion of sperm abnormalities. Nongonococcal urethritis (NGU) is the most common clinical genital syndrome seen in the male. Both acute and chronic infection can cause

partial or complete obstruction of sperm transport (oligozoospermia or azoospermia). Chronic inflammatory changes in the seminiferous tubules in orchitis expected to disrupt the normal process of spermatogenesis and cause alterations in sperm number and quality [24].

Inflammation may act as a co-factor of infertility. Pressure-induced rupture of the epididymal duct will disrupt the blood–testis barrier, activate an immunological defense reaction, and induce the production of antisperm antibodies (ASA) [26]. Kokab et al. found that men infected with *C. trachomatis* had lower percent progressive sperm motility, a higher leukocyte count, and a raised concentration of interleukin (IL)-8 in semen compared with men without infection [26]. Mazzoli et al., 2010 [26] demonstrated that there is a correlation between *C. trachomatis* infection and some important sperm parameters, such as sperm concentration and motility. The attachment of *C. trachomatis* to human spermatozoa was first observed immunofluorescence tests and transmission electron microscopy. Sperm penetration tests revealed that spermatozoa, while progressing forward, can carry chlamydiae attached to them [26]. Chlamydial pathology may alter male fertility since male genital organs are potential targets for CT [28].

Numerous different causes have been observed to affect the sperm, including reactive oxygen species (ROS) generation and the induction of sperm apoptosis. Other causes include cigarette smoking, malignancies, elevated body mass index, insulin-dependent diabetes, drugs, and increasing male age [26].

3.3.3. *Mycoplasma genitalium*

MG is a member of Mollicutes class, which is of 0.3 µm in diameter and it lacks a cell wall. MG is one of the smallest self-replicating organisms usually present in the human genital tract [25]. In 1981, MG was first isolated from the urethra of two men with NGU. MG is considered as sexually transmitted infection (STI). Even though there is no STI symptoms associated with MG, there is a strong association found between risky sexual behavior and MG infection. It is also found to be strongly associated with area-level deprivation and ethnicity having high range of sexual risk behaviors. Sonnenberg et al [29] in 2015 reported high prevalence of MG infection in the United Kingdom at 2.1% in men aged 25–34 years, whereas in women, prevalence peaked at 2.4% in 16–19 years old and decreased with age.

3.3.4. *MG and male infertility*

It is suggested that 15% of male infertility is related to genital tract infection. The prevalence of MG in male of infertile couples found to be higher than normal. The impact of MG infection on male infertility remains unclear.

3.4. Urinary tract infection by *Streptococcus faecalis*

The incidence of oligozoospermia and teratozoospermia was significantly ($P < 0.05$) higher in men whose semen samples contained *S. faecalis* [30]. *Enterococcus faecalis* are associated with poorer semen quality and may warrant treatment [31].

3.5. Hepatitis B viral infection leading to infertility

Hepatitis B virus (HBV) belongs to the class of Hepadnaviridae has a partially double-stranded DNA. HBV is 42 nm in size, and it contains a surface antigen called hepatitis B surface antigen (HBsAg) and the lipoprotein coat [49]. HBV found to be in the blood either in free form, which is predominate, or a viral particle bound protein form [32].

HBV infection is one of the threatening viral infections causing liver diseases in patients. According to Ocama *et al* (2005), approximately 2 billion people worldwide have been infected with HBV, and around 400 million live with chronic infection [33]. China, with a prevalence of 9%, has the highest rate of HBV infection in the world. The prevalence of HBV infections in the Netherlands is 2.2% in 184 men [34]. More than 300 million people in the world are affected with chronic HBV [35].

Hepatitis is an inflammation of the liver, initially recognized as an illness causing jaundice. There were two types of hepatitis: infectious/epidemic hepatitis and serum hepatitis. The HBsAg is responsible for serum hepatitis, which is an envelope protein present in HBV. Epidemic hepatitis is caused by hepatitis A virus (HAV). There are other viruses, namely hepatitis C virus (HCV), hepatitis delta virus (HDV), and hepatitis E virus (HEV) [36].

3.5.1. HBV and male infertility

Hepatitis viruses may cause diseases, which can be acute or chronic [37]. HBV antigens were detected in human semen [38], and it is well established that this biological fluid is a vector for the spread of HBV [39, 40]. There is an evidence that HBV can be transmitted via germ line [41]. The genital tract may act as a reservoir and this infection may get transmitted sexually.

HBV infection was found to be associated with reduced sperm function [42], instability of sperm chromosome, and impaired sperm viability and normal morphology. Recently, HBV DNA and RNA was detected in oocytes and embryos from HBV discordant couples, confirming the possibility of vertical transmission of HBV via germ line during IVF. However, the impact of HBV infection on pregnancy rate and live birth rate is still controversial.

3.6. Small pox, mumps, measles, and tuberculosis infections leading to infertility

Mumps is a condition caused by an RNA virus of the paramyxovirus group. In men, orchitis is the most common complication. Orchitis develops in 5–37% of all adult patients infected with mumps [43]. This causes testicular atrophy in 40–70% of patients with orchitis [44]. Orchitis can be unilateral or bilateral. Bilateral orchitis leads to oligospermia and testicular atrophy in 13% of those patients [45].

4. Symptoms, diagnosis and treatment of the infection

CP due to CT infection is found to have a significant impact on young male fertility. The main challenge in the chlamydial infection is up to 50% men have asymptomatic infection [46]. Many

young people at risk for of CT infection may not seek sexual health care due to the asymptomatic nature of the bacterial infection [47]. HBV infection symptoms include nausea, anorexia, vomiting, flu-like complaints, fatigue, vasculitis, immune complex nephritis, and polyarteritis nodosa. There are approximately 5 % of adults (especially men) develop chronic HBV infection, which is often asymptomatic [32].

4.1. Diagnosis

MG can be found using real-time PCR technique or cell culture. MG culture is time consuming and slow process, and it requires cocultivation in Vero or equivalent cells [26]. Acute HBV infection has an incubation period of 6 weeks to several months. Most of the infected adults will show elevations in Alanine aminotransferase (ALT). Patients with acute HBV infection are mostly seropositive for anti-HBc-IgM antibody, and hepatitis B e antigen (HBeAg) marker correlates with high infectivity. The presence of antibody to HBeAg (anti HBe) shows a less infectious state and also HBV-DNA in serum or plasma indicates active HBV infection [50].

4.2. Treatment

Antibiotic therapy in the eradication of *C. trachomatis* infection does not always result in recovery of semen quality. Prulifloxacin is a drug used to treat patients with CP. Combination of antibiotic drugs and phytotherapeutic agents, such as FERTIMEV, can improve the clinical efficacy of prulifloxacin. l-arginine, l-carnitine, and acetyl-l-carnitine are found to be effective in increasing semen quality, can stimulate the activity of endothelial nitric oxide (NO) synthase, and can enhance sperm motility and function. NO synthase appears to be involved in sperm motility, metabolism, and capacitation. l-arginine in spermatozoa is a source of NO [29].

Based on Centers for Disease Control and Prevention and the Australasian Sexual Health Alliance, 1 g of azithromycin is generally recommended as standard treatment for MG due to its superior cell penetration efficiency. There is an association between MG organism load and azithromycin treatment failure [50]. However there is also an evidence of azithromycin, treatment failure is found due to macrolide resistance mutations. Single nucleotide polymorphisms (SNPs) in region V of the 23S rRNA gene of MG were found to be strongly associated with increased MICs to azithromycin in clinical isolates and treatment failure [28]. Moxifloxacin, doxycycline, gatifloxacin, and sitafloxacin are used as second-line treatment for MG [48]. However, its considerable expense and risk of serious adverse events, including hepatotoxicity, make this agent unsuitable for initial treatment. Recent study shows that single-dose azithromycin therapy is better than doxycycline therapy in the treatment of MG [51].

Lamivudine, one of the novel antiviral agents, is a deoxycytosine analog, which inhibits HBV DNA synthesis and suppresses serum HBV DNA levels in chronic hepatitis B (CH-B) patients. A significant enhancement in CD4-mediated T cell response to HBV nucleocapsid antigen was detectable after lamivudine treatment. One of the most effective treatments for CH-B is interferon (IFN) therapy [35].

Active vaccination is highly effective in preventing HBV infection. *Active prophylaxis* is a recombinant vaccine. Recombivax HB and Engerix-B are the commercial products available

[32]. Successful vaccination strategies have led to significant decrease in HBV prevalence [36]. In case of adult patients, 90% of them recover from HBV infection. However, 90% HBV-affected children ≤ 4 years of age develop chronic infection [32].

5. Conclusion

Microbiota refers to the microorganisms present in a particular site. Microbiota when is disrupted can cause infection on that site. Male genital tract infections are one of the reasons for male infertility, which can be prevented by proper sanitation. Proper precaution and awareness should be exercised among population.

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