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LETTERS

Current perspectives of Male Infertility induced by Immunomodulation due to Reproductive Tract Infections

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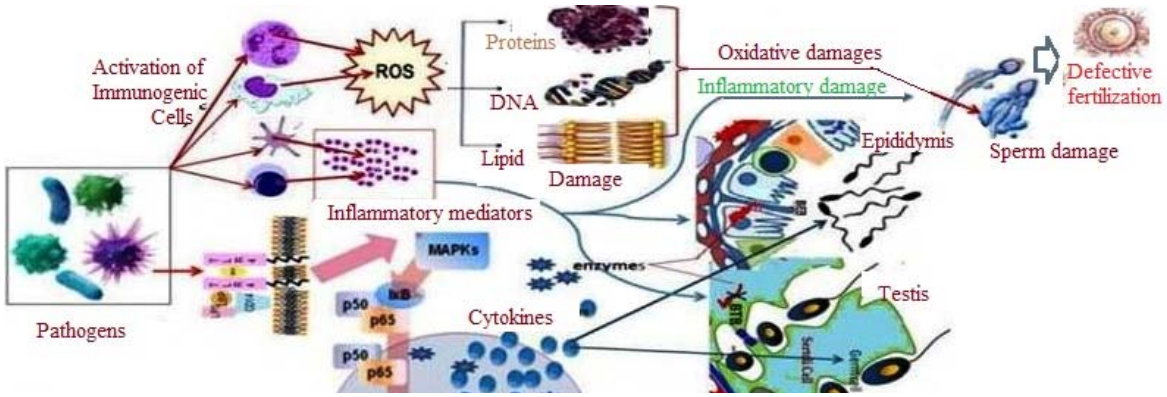
ABSTRACT



Globally, approximately 15% of couples of reproductive ages suffer from reproductive sterility. Almost half of such cases involve male sterility which is normally an asymptomatic condition, and, in most cases, the condition is reversible with proper treatment. Uropathogens and ascending sexually transmitted infections (STIs) are recognized as one among many other causes of inflammatory diseases of male genital tract which in turn are common reason of male infertility. Thus, any suspicion of inflammatory infection of the male genital tract should be immediately diagnosed Followed by further clinical evaluation in order to rule out any pathogenic situation due to infection of male genital tract which can lead to male sterility. Proper recognition and timely treatment can help to overcome such problem.

Keywords: ascending sexually transmitted infections, infertility, inflammatory diseases, reproductive sterility, uropathogens

INTRODUCTION

Incidence of male infertility is showing an increasing trend and is above 50% globally. Male urinary tract infection accounts for 10% cases of male infertility.[1] The pathogens including bacteria, virus, fungi and parasites have their individual distinct pattern for building up such problems. These organisms affect organs like the testis, epididymis and accessory sex glands. The infections may be acute or chronic and is known to effect male fertility adversely. Production of normal and healthy sperm is one of the prime determining factors of male fertility. The process of spermatogenesis is regulated by various factors and their synchronization. Presence of pro–inflammatory cytokines, tumor necrosis factor-alpha (TNF–α), interleukin–1 alpha (IL–1 α) and interleukin 1 beta (IL–1 β) cytokines in normal level in the male reproductive tract (testis, epididymis and sperm) are necessary for normal physiological functions. Infection and inflammation of the male genital tract causes production of several proinflammatory factors in profuse which is higher than their normal physiological level and is very harmful for production of sperm.[2] Thus, Infection and inflammation of the male reproductive tract deteriorates the spermatozoa function,

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testicular spermatogenesis leading to sperm alterations qualitatively and quantitatively.[3] Such pathogens and their mechanisms are highlighted in the tables below (Table 1-3).

Table 1. Bacterial pathogen, characteristics, target cell mechanism of infection and outcome.

Pathogen Characteristics and target cell infection	**Mechanism of Action and Effects**
Chlamydia trachomatis Gram negative bacterium. It belongs to a group of obligate intracellular prokaryotes. They replicates only inside a vacuole, termed inclusion, in the cytoplasm of the host cell. They mostly target mucosal epithelial cells	Specific lipopolysaccharide (LPS) antigen leads to histopathological alterations of ejaculatory ducts involving loss of stertiocilia damaged canalicular system of male genital tract lingering to obstructive azospermia. It interacts with CD14 on sperm surface leading to increased production of ROS and caspase mediated sperm apoptosis. Altered tyrosine metabolism and defective sperm capacitation, reduced sperm motility and defective acrosomal reactions[3] **Effects:** Urethritis, epididymitis, epidiymo-orchitis, prostatitis and enlargement of seminal vesicles.
Neisseria gonorrhoeae Gram negative, diplococci. They usually target non ciliated epithelial cells through pili and release lipopolysaccharide endotoxin.	Lipooligosaccharide of pathogen membrane reacts with asialoglycoprotein receptor of spermatozoa leads to production of the inflammatory cytokines IL-6, IL-8, and TNF-α that may sperm cell apoptosis.[4] **Effects:** Urethritis, prostatitis and epididymitis.
Pseudomonas aeruginosa Gram-negative, opportunistic bacterium rod-shaped, asporogenous, and monoflagellated bacterium. Usually infects epithelial cells of target host with fimbriae and release proteases that help target cell infection.	3-oxododecanoyl-L-homoserine lactone, have detrimental effects on spermatozoa, pathogen porins induces apoptosis to sperm cell line and chromatin abnormalities of sperms.[5] **Effects:** Sperm abnormality and oligospermia
Ureaplasmaurealyticum Smallest free-living pleomorphic bacteria that lack a cell wall. They usually colonize extracellularly in genital tract and infects host cell by toxic metabolic products.	Metabolic products of the pathogen like reactive hydrogen species kill sperms. Seminal viscosity is increased, semen quality is detracted and sperm motility and density is also reduced. **Effects:** Nonchlamydial, nongonococcal urethritis, prostatitis, epididymitis, oligospermia.
Escherichia coli Rod-shaped Gram-negative bacterium. They adhere host uro-genital epithelial cells by type-I fimbrae and release certain virulence factors including LPS and porins that infect host epithelial cells.	LPS and porins of the organisms bind to spermatozoon. Direct interaction of bacterial pili with the sperm plasma membrane alters sperm motility, affects spermatozoa by action of soluble factors that induce apoptosis and a breakdown in the mitochondrial membrane potential ,activation of several caspases and proteases responsible for mitochondrial changes; alterations in membrane symmetry; and DNA fragmentation and apoptosis.[6] **Effects:** Epididymoorchitis, acute or chronic prostatitis.
Treponema pallidum motile spirochete, helically shaped microaerophilic bacterium that lack lipopolysaccharide.	Specific tpr genes encode proteins that mediate attachment to host genital epithelial cells and functions as poins to invade host eithelial cells. Syphilytic epididymis may be assisted with chronic obliterative endarteritis and interstitial inflammation and fibrotic testis and loss of testicular function.[7] **Effects:** Orchitis (predominantly granulomatous), Syphilitic epididymitis

Table 2. Viral pathogen, characteristics, target cell mechanism of infection and outcome

Pathogen Characteristics and target cell infection	**Mechanism of Action and Effects**
Herpes Simplex Viruses Caged Double stranded DNA virus. Usually invade host epithelial cell to enter nucleus. They carry out genomic replication, transcription and caspid assembly that produces new viron which is released from host cell to infect further.	Leads to seminal tract infection by release of proinflammatory cytokines and ROS that damage fertility by decreasing polyunsaturated fatty acid (PUFA) on sperm membrane impairing acrosomal reaction and DNA damage. Thymidine kinase expression by a strain of this virus is related to degeneration of spermatogenic cells, failure of Sertoli cells and germ cells homeostasis and loss of germ cells that may involve apoptotsis.[8] **Effects:** Oligospermia.

Human Papilloma Viruses (HPV) Double-stranded non enveloped DNA adenovirus. The virus enters target host cells and enters nucleus to carry out its own replication. α TIF and other viral proteins assists in host cell infection	HPV infection is related to anti-sperm antibodies (ASAs) which may reduce male fertility by interfering with sperm motility and sperm-oocyte binding assisted by release of cytokines that can weaken sperm function.[9] **Effects:** Azoospermia
Human Immunodeficiency Virus Single stranded RNA virus. It suppresses the immune system by infecting CD4 T cells by using target cell machinery to synthesize its own genome	Immune suppression related low serum testosterone level, leads to secondary hypogonadism followed by low sperm production. Moreover, nucleosidic reverse transcriptase inhibitor may lead to sperm mitochondrial damage and impaired sperm production.[10,11] **Effects:** Orchitis, lower ejaculation volume, sperm count, and progressive motility.

Table 3. Other pathogens, characteristics, target cell mechanism of infection and outcome.

Pathogen Characteristics and target cell infection	**Mechanism of Action and Effects**
Candida sp. Opportunist yeast They adhere to the surface of epithelial cells by special cell surface adhesion molecule and forms biofilm. Thereafter they invade genital epithelial cells and endothelium by Als3 proteins.	Adherence of spermatozoon on the microbe leading to sperm agglutination and immoblilization, acidic protease and phosphatidase released also deforms sperm ultrastructure.[12] **Effects:** inhibitory effect on human sperm motility and impairs the ultrastructure of human spermatozoa.
Trichomonas vaginalis Flagellated protozoan parasite. The adhere to host epithelial cells by specific cysteine proteases that helps in attachment to host genital squamous epithelial cells and release extracellular protease that injure the epithelial cells	Proteinases released by pathogen inhibits sperm motility. Other extracellular polymeric substances released may cause inflammatory change in genitourinary tract and impairs sperm motility, viability and functional integrity in experimental animals.[13] **Effects:** Nongonococcal urethritis, epididymitis, prostatitis, and other genital tract disorders

These tables data, thus, indicate that pathogens interfering with male fertility may affect the male reproductive tract in different ways. The chief mechanisms involved and recognised are immunological interventions, autoimmune mechanisms, sperm immune reactions, genetic abnormalities[14] and defects in sperm receptor ligand interactions.[15] Some of the immunological mechanisms are considered and discussed in this review article.

Pathogens which are specialised to infect men and to colonise the genital region cause sexually transmitted disease (STD).[16] STD causing pathogens are associated with male sterility. Some sexually transmitted infections may not cause infertility while some may. The mechanism is specific for each pathogen. Other non-sexually transmitted infections like leprosy, tuberculosis may also cause male sterility.[17] Urethral strictures and epididymo-orchitis may be caused due to chronic infections like gonorrhoea etc.[17] Chances of transmission of the human immunodeficiency virus (HIV) increases with any kind of STDs. The HIV infection has been reported to be associated with infectious semen and the risk of virus transmission. Semen quality deteriorates with the progression of immunodeficiency.[16]

The Testicular Immune Responses to Pathogens

The mammalian testis has a special immune environment due to its two characteristics: (a) the immunogenic germ cells in testis are protected from detrimental immune attack and (b) the **testis** adopts potential local innate defense mechanisms against microbial infections.[18] Normally the testis has two compartments: the seminiferous tubules and the interstitial section in conjunction with blood vessels. Moreover, blood testis barrier provides defence against invading cells and pathogens. The immunogenic cell of the testis includes macrophage, minor dendritic cells, T lymphocytes and mast cells. Under normal hormonal milieu the Sertoli cells privileges testicular immune suppression by regulating the activities of the above immunogenic cells by paracrine mechanisms.[19] Urinary tract infections (UTI) by pathogenic bacterial LPS releases proinflammatory cytokines tumour necrosis factor (TNF) and interleukin 1 beta (IL1B), reactive oxygen species, nitric oxide (NO) and corticosteroids that affects the hormonal milieu which declines the androgen production that may be sufficient for causing spermatogenic disruption. Toll like receptors present in the Sertoli cells have a unique property of recognizing bacterial LPS, peptidoglycans and viral and bacterial nucleic acids that activates inflammatory signalling pathways leading to the mitogen-activated protein (MAP) kinases and the expression of inflammatory transcription factors, nuclear factor kappa B (NFkB), and interferon regulatory factor 3. This may lead to expression of major pro-inflammatory factors, including IL-1, IL-6 expression, nitric oxide synthase-2 and TNF-α, especially IL1-α that mediates inflammation in the testis by opening blood testis barrier followed by IL1-β upregulation that may be harmful for testicular spermatogenesis. The inflammatory cytokines IL-6 increases in ED1+ macrophages that affect germ cell apoptosis and sloughing of Sertoli cells. Regulatory T cells alone may not be able to limit excessive T-cell activation leading to autoimmune orchitis. Altered Cox2 and prostaglandin expression from testicular mast cells is also emerging condition for fibrosis and altered spermatogenesis.[20] On the other hand, it is also reported that activation of toll like receptors namely,

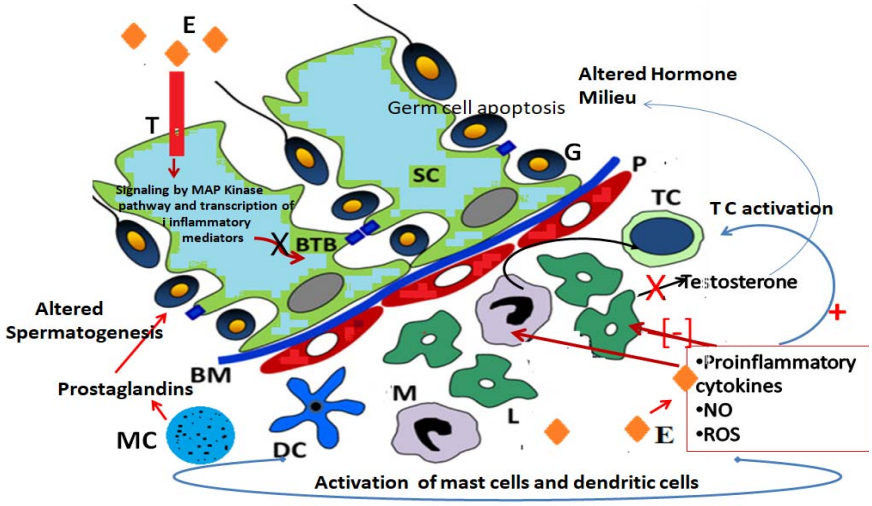

Figure 1. The testicular immune responses to pathogens. B, Basement membrane;BTB, Blood testis barrier;DC, Dendritic cell, E, Pathogenic endotoxin [bacterial LPS, peptidoglycans and viral and bacterial nucleic acids];G, Germ cell;L, Leydig cell;M, Macrophage;MC, Mast cell;P, Peritubular cell;T, Toll like receptor;TC, T cell;SC, Sertoli cell.

TLR3 and TLR4 in the Leydig cells suppresses steroidogenesis by Leydig cells.[21]

Studies show that stimulation of testicular toll like receptors TLR2/TLR6 and TLR5 induces increased ICAM-1 expression in Sertoli cells. The presence of TLR2, TLR4, TLR5, and TLR6 were found in the seminiferous tubule. Those toll-like receptors are the ones that mediate the innate immune response against all species of bacteria i.e., Gram-positive (TLR2/TLR6), Gram-negative (TLR4), and flagellates (TLR5).[22]

It has been reported that inflammatory responses in the testis is induced by damaged germ cells. Male germ cells are known to secrete various cytokines like IL-1α and TNF-α, and thus germ cells may function in regulating the immune response.[18]

Pathogenic endotoxins releases proinflammatory cytokines, NO and ROS that affect Leydig cell function and hinders testosterone release.[23] This may alter the hormonal milieu essential for germ cell development. The pathogenic toxins also activate dendritic cells and mast cells. The later alters Cox and prostaglandin expression that further amend the process of spermatogenesis. In addition, such toxins also bind to Toll like receptors of Sertoli cells so as to trigger MAP kinase signalling pathway leading to increased synthesis of inflammatory mediators ultimately ending up in blood testis barrier destruction (Figure 1).

Immune Mechanisms Involved in Epididymitis

The epididymis has highly organized orientation of immune cells including blood epididymal barrier critical for male fertility.[24] Macrophages in epididymis express major histocompatibility complex (MHC) class II antigens,[25] required for antigen presentation to restricted $CD4^+$ T cells (helper and regulatory T cells) that predominate over the $CD8^+$ (cytotoxic) T cell subset. Antigen-presenting dendritic cells and basal cells are other immune modulatory cells. indoleamine 2,3-dioxygenase (IDO) and pro-inflammatory cytokine are some immunomodulatory substrates.[26] IDO is regulated through the SMAD2/3/4 signaling pathway that is activated by activin A which involves the intervention of androgens14. The pathogen-sensing Toll-like receptors (TLRs)2,7,9,11 and TLR4 co-receptor CD14 are highly expressed in epididymis. TLR2 and TLR4 and CD14, a 54 kDa protein, part of the bacterial LPS-receptor complex may involve a reaction cascade with immunogenic cells, dendritic cells and modulate the levels of Il-6, Il-17, Il-23, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and neutral α-glucosidase that may destroy blood epididymal barrier leading to further pathogenic infiltrations affecting sperm structure and epididymal integrity this may be followed by further antigenic challenge, macrophage activation. Spermatic granulomas formation comprised of disintegrating spermatozoa, macrophages, neutrophils, and vacuolated epithelial cells containing cellular debris.[26]

Pathogenic toxins and metabolites activated dendritic cells with via activin assisted SMAD2/3/4 signalling increases the expression of IDO. IDO attenuates immune response and helps in colonization of pathogens in epithelial cells. Further these toxins activate macrophage –T cell cascade leading to additional release of proinflammatory cytokines. Activation of Toll like receptors of epididymal cells by pathogenic substrates induce MAP Kinase signalling pathway and increases the expression of inflammatory mediators, TRIAL and α glucosidase.[27,28] The later causes destruction of BEB and infiltration of pathogens which directly affect sperm cells within epididymis (Figure 2).

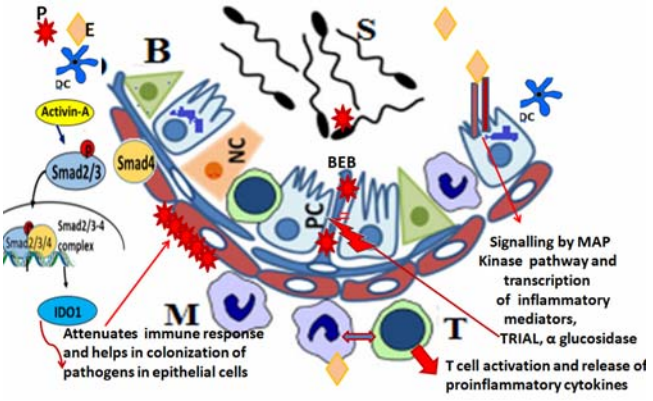

Figure 2. Immune mechanisms involved in epididymitis. B, Basal cells; BEB, Blood Epididimis Barrier; DC, Dendritic cell; E, Pathogenic endotoxin [bacterial LPS, peptidoglycans and viral and bacterial nucleic acids]; M, macrophage; NC, narrow and clear cells; P, Pathogen; PC, Principal Cells; S, Sperm; T, T cell; IDO1, indoleamine 2,3-dioxygenase.

Immune Consequences in Sperms

It has been suggested that activation of γδ subset of T lymphocytes by pathogenic infection initiates development of an autoimmune response to spermatozoa within male genital tract.[29,30] HSP 60 is released from bacterial component leads to activation of γδ subset of T lymphocytes and is a potent cytokine inducer.[29] *C.trachomatis* infection leads to local activation of γδ T cells, which in turn stimulate lymphocytes possessing the αβ subset T cells finally generating autoimmune response to spermatozoa.[31] In addition, other microbial pathogens may induce auto active T cells to sperm antigens. INF-γ, TNF-α and cytokines may assist in this process. INF-γ interfere with sperm motility by damaging the structural integrity of plasma membrane and TNF-α suppresses sperm mitochondrial protein synthesis. Some microbial[32] pathogens may affect the sperms; pursue the expression of some surface virulent factors like lipopolysaccharides (LPS), cytotoxic necrotising factor, α-haemolysins and ß-haemolysins, and release of soluble spermatotoxic factors such as sperm immobilisation factor (SIF).[33] Bacterial infection of Urinogenital tract most likely attracts leukocytes to the semen are phagocytic cells such as polymorphonuclear granulocytes (PMNs) and macrophages decrease sperm count, increase abnormal sperms, impair viability, decline motility, and reduce penetration rates in cervical mucus. Moreover, the tight bonding of neutrophils and macrophages to the surface of the sperm, increase production of Reactive oxygen species (ROS) like superoxide anion,[34] hydroxyl radical etc. affects sperm function, membrane lipid peroxidation, sperm DNA fragmentation, disrupted seminal homeostasis ending up to sperm phagocytosis.[35,36]

Sperm motility is dependent on mitochondrial function.[37] Bacterial and viral pathogens may lead to mutated mitochondria DNA in semen of patients with UTI.[38] ROS generated from anaerobic metabolism of microbes may lead to DNA fragmentation of mitochondria.[39] Such mitochondrial genomic modification may lead to a defective mitochondrial respiratory chain function and improper energy production that is essential for sperm motility.[40] In addition, recently it has been also been reported that TLR activation in sperm by pathogens reduces sperm motility via signalling through myeloid differentiation factor 88 (MyD88), phosphatidylinositol 3-kinase (PI3K), and glycogen synthase kinase (GSK)-3α.[40]

Pathogens may act directly on sperms or indirectly by the release of toxins and metabolites may active immunogenic cells like neutrophil, macrophage, T cell, and dendrtitic cell leading to production of a disbalance in pro-oxidant and antioxidant. This may increase the oxidative damage of sperms as mentioned in the figure leading to sperm death and sperm loss (Figure 3).

Genetic Abnormalities by Pathogens for Male Infertility

As reviewed above, bacterial infections followed by inflammatory mechanisms have been associated with male infertility. Although acute infection is not morbid chronic urinogenital pathogenic infection las long last negative impact

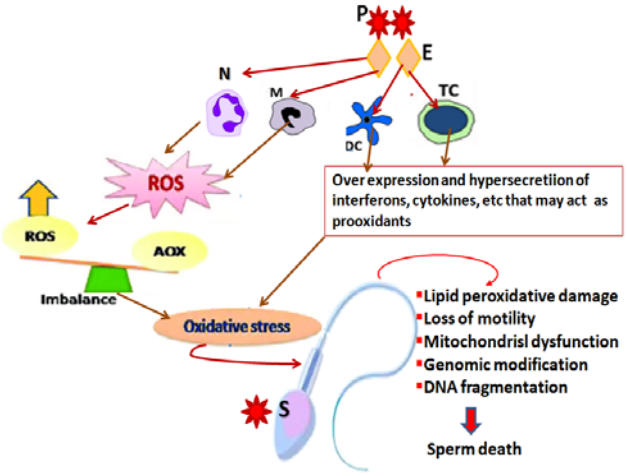

Figure 3. Immune consequences in sperms. AOX, antioxidant; DC, Dendritic cell; E, Pathogenic endotoxin [bacterial LPS, peptidoglycans and viral and bacterial nucleic acids]; M, macrophage; N, Neutrophil; P, Pathogen; ROS- Reactive oxygen species; S, Sperm; TC, T cell

on male fertility.[41] Pathogens that colonize in the male urinogenital tract may have some impact on genomic stability.[42] Although the exact molecular mechanism of such genomic interference has yet to be studied, epigenetic mechanisms involved in such cases may not be overruled. In human post-meiotic spermatogenesis involves chromatin packing and compact reorganization that involves the role of histones.[43] The bacterial infections lead to early emergence of histone H3 methylation at lysine 79 (trimethylated H3K79) and hyperacetylated H4 that simultaneously occurred with transition protein TNP1.[44] Reduced levels of histone H4 hyperacetylation in mammals is also reported to be associated with impaired fertility.[45–47] Further, lack of DNA repair mechanisms in spermatids and spermatozoa may increase sperm defects in human urinogenital tract.[48,49]

Consequences on Sperm Receptor Ligand Interaction

Primary step in fertility is the search for the oocyte by spermatozoa. Male fertility also involves the capability of sperms to interact with oocyte and consequently successful fertilization. Many surface proteins like CD46, ClqR, Fibronectin, Laminin, Vitronectin etc. of sperms may help in sperm adherence to endometrial or tubal epithelium and assisting travelling of sperms in female genital tract. However, expressions of these proteins are regulated by the testis and inflammatory conditions or infections by pathogens may impair expression of such substances. In addition sperm chromosomal decondensation, defective chromosomal packing and DNA fragmentation by pathogens may lead to formation of immature sperm surface proteins that may lead to defective sperm oocyte fusion. Oxidative stress, leading to production of reactive oxygen species either by pathogenic metabolism, or pathogen-immune cells interactions, may be involved in the defective

fertilization. Autosperm antibodies specific to sperm heads may also behold sperm-oocyte receptor ligand interactions.[50]

CONCLUSION

Infection of the genital tract can thus cause male infertility which in many cases may go undetected if not investigated. Any kind of infection, even an infection which may not cause severe inflammation may lead to blockage of the male ejaculatory duct and induce infertility. Inflammation which may not be due to infection may also cause male infertility. In rare instances, chronic prostatitis is one such condition which can block the male ejaculatory duct and lead to infertility. On the other hand pathological conditions like prostrate hyperplasia may block the male genital tract and thus lead to infertility. Treatment of such infection mediated inflammation induced male infertility generally involves administration of non-steroidal anti-inflammatory drugs which basically mitigates the inflammation and the pain caused due to inflammation. Antibiotics are also used which may completely cure the infection but, in some cases, infection induced male infertility may not get reversed. Thus treating infection and inflammation may not always restore fertility. Sperm retrieval techniques are often utilised to deal such conditions where sperm is absent in the ejaculate. Sperm is directly collected from the seminiferous tubules of the testicles or the epididymis in such cases and *in vitro* fertilization is followed. Proper recognition of the pathological condition which is underlying the situation of male infertility is needed. Understanding of the male reproductive inflammatory conditions and the associated infection mediated inflammatory complications should be addressed while diagnosing male reproductive sterility. Follow-up treatment is utmost necessary to deal infection mediated inflammation induced male sterility.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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