Chem. Biol. Lett. 2020, 7(2), 75-84 Article

Chemical Biology
LETTERS

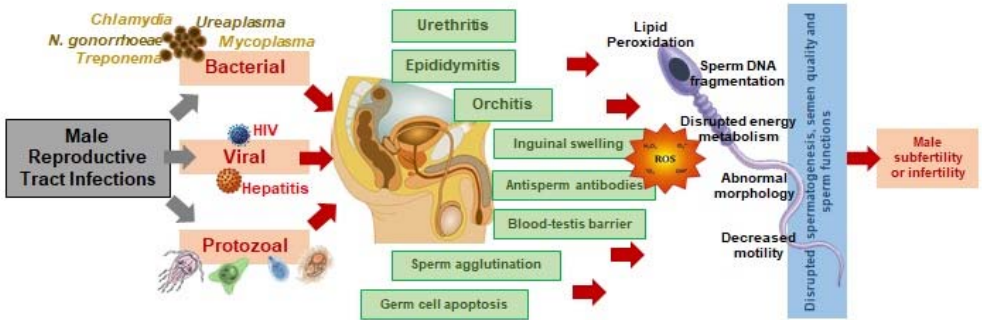
Reproductive tract infection, inflammation and male infertility

Pallav Sengupta,[1] Sulagna Dutta,[2] Ahmed T Alahmar,[3*] Urban John Arnold D'souza[4]

[1]Faculty of Medicine, Bioscience and Nursing, [2]Faculty of Dentistry, MAHSA University, Malaysia. [3] College of Medicine, University of Babylon, Iraq. [4]School of Medicine, Universiti Malaysia Sabah, Malaysia

Submitted on: 17-Jan-2020, Accepted on: 26-Feb-2020 and Published on: 16-Mar-2020

ABSTRACT



Infection or inflammation in the reproductive tract either via pathogenic intrusion or systemic diseases, reportedly are closely associated with deterioration in male fertility parameters. There are various proposed mechanisms to explain how reproductive tract infection or inflammation may curb male fecundity. One of the prominent mechanisms is via the over-production of reactive oxygen species (ROS) inducing testicular oxidative stress (OS). In normal conditions, testicular cells produce ROS at modest levels to maintain physiological functions. However, in inflammatory state, the surge of pro-inflammatory mediators, cytokines lead to infiltration of immune cells (as observed by increased seminal leukocytes number) and these leukocytes serve as major contributors in the increased seminal plasma ROS levels that overwhelm the testicular antioxidant capacities. This initiates oxidative damage to the testicular cells to impair sperm production, as well as sperm membrane damage, disruption of essential signalling cascades, sperm mitochondrial and nuclear DNA damage and thereby impairing overall sperm functions. There are number of studies reporting diversified hypothesis of infection/inflammation-induced male reproductive problems. This article aims to review the available information and present a precise overview of possible mechanisms relating male reproductive tract inflammation and male infertility.

Keywords: cytokines, infection, inflammation, leukocytes, oxidative stress, semen quality

INTRODUCTION

A couple may be considered infertile when they fail to conceive even after regular unprotected sexual intercourse for a period of one year.[1] Almost 15% couples are infertile among all sexually active ones.[2] In isolation, or combination with a female element, the male factor represents about 50% of the infertility cases.[1, 3]

There can be varied causes for infertility.[4-9] The reproductive system of both sexes can be compromised by infectious agents. It is estimated that approximately 15% of male infertility is caused by male genital urinary tract infections,[10] affecting different sites of male reproductive system, such as testis, epididymis, and male accessory glands.[11]

Spermatogenesis itself may be impaired at different levels of sperm production, maturation and transport by urogenital infections, which can either be sexually transmitted or non-sexually transmitted.[11] *Chlamydia trachomatis* and *Neisseria gonorrhea* are of the most common sexually transmitted microorganisms that interferes with male fertility.[12] Male infertility is less frequently caused by epididymo-orchitis which

*Corresponding Author Dr. Ahmed T Alahmar
College of Medicine, University of Babylon, Iraq
Tel. +9647808180900
Email: ahmed.t.alahmar@gmail.com

Cite as: *Chem. Biol. Lett., 2020, 7(2), 75-84.*
URN:NBN:sciencein.cbl.2020.v7.108

 ISSN: 2347–9825 http://thesciencein.org/cbl

is primarily transmitted in nonsexual ways by *Escherichia coli*. Lower genital tract infections tend to have low importance. These and other male-genital urinary-tract infections can, however, contribute to a microbial infiltration and colonization in seminal plasma.[12-14]

Different mechanisms are proposed to explain how infection or inflammation in the reproductive system can reduce male fertility.[14-16] One of the prominent mechanisms involve induction of testicular oxidative stress (OS) through overproduction of reactive oxygen species (ROS).[17-19] Testicular cells produce ROS to maintain their physiological function at modest levels, in normal conditions.[17,20] In inflammatory state, however, cytokines and inflammatory mediators lead to immune cell infiltration (evidenced by increase in the number of seminal leucocytes)[14] and these leukocytes serve as major contributors[21,22] in the increased seminal plasma ROS levels that overwhelms the testicular antioxidant capacities. This initiates oxidative damage to the testicular cells to impair sperm production, as well as sperm membrane damage, disruption of essential signalling cascades, sperm mitochondrial and nuclear DNA damage and thereby impairing overall sperm functions.[13,17, 23]

There are several studies which report diversified hypotheses of male reproductive problems caused by infection/inflammation.[12,21] This article aims to review the information available and present an accurate overview of the possible mechanisms for male reproductive tract infection-induced male infertility.

Reproductive Tract Infections and Male Infertility

Lack of conception in a period of one year with repeated unprotected coitus among couples is defined as infertility. Generally, the cause for underlying infertility may be due to non-physiological to pathological conditions prevailing in either male or female and many a time among both. In male partner few causes that may lead to infertility include, endocrine hormonal disorders, metabolic causes, genital infection that lead to semen infections, obstruction in genital tract and many more.

Variety of micro-organisms may lead to infertility among male population. Microorganisms generally colonize in the semen irrespective of their origin of infection either in the main genital tract or genitourinary tract of the male. Bacterial agents such as genital mycoplasmas generally invade the genital tracts such as *ureaplasma urealyticum* and *mycoplasma hominis.*[24] Urethritis, prostatitis and few instances orchitis are caused due to *Ureaplasma urealyticum* or may be *Mycoplasma hominis*. It is further confirmed that ureaplasmas are causing non-chlamydial, non-gonococcal urethritis in males.[25] But many studies revealed that *M. hominis* and *U. urealyticum* have not caused the decline in the quality of sperm but incubation with *M. hominis* has resulted in adverse effect on sperm motility, morphology and fertilizing potential. Elevated concentrations of granulocyte elastase in the seminal plasma are the confirmatory factors those are the indicators of male genital tract infections and around 20-30% infertile men have silent genital inflammations according to the WHO.[26,27] Changes in sperm characteristics and apoptotic markers, semen contamination by excess leucocytes as an outcome of inflammation in the male genial tract in addition toxic reactive oxygen species (ROS) depending on the infectious agents were implicated as the possible factors that contribute for the infertility among the male population.

Bacterial infections

Mycoplasma

Two mycoplasma species are clinically relevant. These are *M. genitalium* and *M. hominis.*[24,28] Mycoplasma infections are prevalent at 4.8 percent for *M. genitalium*, and 9.6 percent for *M. hominis.*[29] Of the men with persistent urethritis, 41 percent are positive for *M. genitalium.*[30] These infections reduce sperm motility and morphology and can induce sperm DNA damage.[24,31] Gallegos et al. (2008) reported that high ROS production induced by inflammation is causative of DNA damage in mycoplasma- infections. Sperm DNA damage reduced significantly following a course of antibiotics and anti-inflammatory steroids ($p < 0.001$).[32]

Ureaplasma

Ureaplasma urealyticum and *Ureaplasma parvum* are the two clinically significant ureaplasma species which are accountable for male infertility with an incidence of 15.6% and 2.9% respectively.[29] Infection rates for ureaplasma in patients with male infertility range between 5% and 42%.[33] While sperm motility and normal sperm morphology reduce, damage to sperm DNA elevates. Because ureaplasma does not cause an inflammatory process that would degrade the quality of semen,[34] it remains unknown why these semen parameters deteriorate.[24,34] These pathogens accrue in the urethra and are likely to bind directly to sperm following ejaculation,[34] a process that is believed to cause increased damage to DNA and loss of membrane integrity through ROS formation.[32]

Escherichia coli

Escherichia coli is the most important bacterium in male infertility caused by infection.[35] *E. coli* reduces sperm motility, decreases vitality, and increases damage to DNA.[36,37] *E. coli*-mediated infertility has many modalities of how male infertility may be caused. For example, *E. coli* induces leukocyte recruitment and thus encourages neutrophilic ROS development.[38] Proinflammatory cytokines, such as IL-6, can break cell membranes directly, decreasing sperm motility.[39] Similarly, the *E. coli* reduces sperm membrane integrity by directly binding to their membrane and adding porins to the membrane of the spermatozoa.[40] Porin formation, in effect, induces cytoplasmic material to be released and contributes to a significant reduction in viability from 80% to 100%. Finally, the attached haemolytic subspecies *E. coli* decreases sperm vitality by decreasing the sperm plasma membrane potential that mediates the production of intracellular ROS.[41]

Viral infections

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) reduces sperm motility, vitality and forward progression once the counts of CD4 cells are less than 350 cells / microliter.[42] Otherwise,

asymptomatic HIV-seropositive people do not display reduced fertility.[42] Recruitment of monocytes, macrophages, and leucocytes in semen is observed in people with symptomatic HIV infections.[42] With existing extremely active antiretroviral therapy (HAART) regimens improving HIV-infected men's life expectancy, research on how HAART affects male fertility reveal a detrimental effect on semen quality.[43] Use of non-nucleoside reverse transcriptase inhibitors can induce oxidative stress because these are mitochondrially toxic[44,45] and damage the mitochondrial membrane potential.[46]

Hepatitis

Both hepatitis B and hepatitis C are viruses which have been shown to cause male infertility. Hepatitis B is known to aggravate parameters of fertility due to its ability to move through the blood–test barrier.[42,47] Given the ability of the hepatitis B virus to move through the blood–testis barrier, it can transmit its genome directly into spermatozoa leading to defective spermiogenesis and lower fertilization levels.[48] Hepatitis B-exposed spermatozoa were identified with increased externalization of phosphatidylserine and assessed lipid peroxidation by MDA formation.[49,50] High seminal concentrations of IL-18 were found in men with chronic hepatitis B, which causes natural killer cells to secrete proinflammatory cytokine INF-ɣ.[50] These authors found a positive association between the formation of inner MDA and the concentration of IL-18, indicating the formation of MDA is caused by an inflammatory process. There is currently no research relating directly to IL-18 and leucocyte activation in the male reproductive tract from hepatitis B infection, however. Transmission of hepatitis C comes primarily from intravenous drug abuse and mother-to-child transmission.[51,52] Concerning the ongoing opiate crisis in the United States, primary opiate abusers are reproductive-age (mean age of 22.9 years) and contribute significantly to increased hepatitis C transmission.[51] The hepatitis C virus, unlike hepatitis B, does not pass through the blood–testis barrier and cannot cause direct oxidative stress to spermatozoa.[42] Infections with chronic hepatitis C induce systemic elevations of TNF-α and NO.[53] As a result, chronic inflammation and lymphocyte activation and polymorphonuclear leucocyte activation appear.[54] Polymorphonuclear leucocytes generate ROS via NOX2, resulting in a loss of the mitochondrial membrane potential in the spermatozoa resulting in further propagation of ROS and OS.[53,54] Hepatitis C-induced OS leads sperm motility to decrease, but unaffected ejaculatory volume, apoptosis and enhanced DNA damage.[53, 54]

Sexually transmitted diseases and male infertility

Sexually transmitted diseases (STD) disrupt either the hormonal axis, spermatogenesis or transport of sperm in the tract. STDs contribute its major share in the male infertility; high titer of seropositive chlamydia antibodies which is a marker of severe infections has contributed for the male infertility.[55] Polymerase chain reaction (PCR) which detects chlamydia, *Mycoplasma hominis*, and *Ureaplasma urealyticum* in semen samples of infertile men was significantly higher compared to the fertile men indicating a strong association of STD infection in the infertility.[56] Lipopolysaccharides extracted from chlamydia have caused a total mortality of spermatozoa in the incubation studies and also a decline in sperm motility.[40] Genital mycoplasma and ureaplasma were proved to be causative agents in male infertility causing declined sperm motility and membrane alterations in addition to DNA damage.[34] Neisseria gonorrhoeae DNA was detected in infertile men semen samples and trichomonas vaginalis has caused a lower sperm motility.[57] In addition, Epstein barr virus, cytomegalovirus, herpes, papilloma virus, hepatitis and human deficiency virus have their chances in causing infertility in men but the association of unknown origin due to STDs has not been extensively studied to arrive at a strong correlation with individualized STD infection and male infertility.

Neisseria gonorrhoeae

The male urogenital tract represents two types of changes after infection - a rise in diameter and a decrease in seminal flow velocity.[58] This will result in elevated ROS levels. The gonorrhoea causative agent, N. gonorrhoeae, can colonize genital, rectal and nasopharyngeal mucosa during infection.[59] Gram-negative bacteria include, N. Gonorrhoeae are unusual in that they produce large quantities of peptidoglycan during development.[60] *N. gonorrhoeae* is capable of activating TLR2, TLR4 and cytosolic receptor nucleotide-binding oligomerization (NOD)-1 and NOD2 in the inborn immune response to the bacterial antigen. This cycle further stimulates the NF-kB transcription factor and the adaptor-receptor-interacting serine–threonine kinase 2 polyubiquitination (RIPK2)[60]. Activation of the NOD receptor suggests that the immune response can trigger not only cytokines (IL-16) and chemokines, but it also induces complement proteins, growth factors (CSF1), and other cytosolic pattern recognition receptors on cell surfaces such as toll like receptors.[60] In addition, IL-1 induces apoptosis in semen through the proliferation and differentiation of B- cells to trigger generations of neutrophils and monocytes with the help of chemoattractors such as IL-8.[58] In N. gonorrhoeae-infection, expression of IL-1 and IL-8 have a significant clinical effect.[61] Duru, Morshedi, and Oehninger (2000) have shown a negative correlation between seminal oxidative stress and concentration, function, and motility of the sperm. Cytokines and adipokines may also be proposed to be the mediator of semen quality and male infertility.[58,62-66] A research further suggests that increased levels of IL-1β were correlated with a reduction in sperm motility and a rise in seminal ROS and malondialdehyde (MDA), a lipid peroxidation by-product.[67]

Chlamydia trachomatis

Chlamydia trachomatis has the greatest prevalence rate worldwide with 4.2% for women and 2.7% for men who are infected[68]. Chlamydia provides people with a clinical problem as 50% of men diagnosed with chlamydia are not being treated empirically.[69] The mechanism underneath male infertility induced by Chlamydia trachomatis remains unresolved. There are currently three main hypotheses: (a) high WBC levels as triggered by cytokines; (b) CD 14 receptor interaction; and (c) antisperm antibodies development.[11] More precisely, this theory

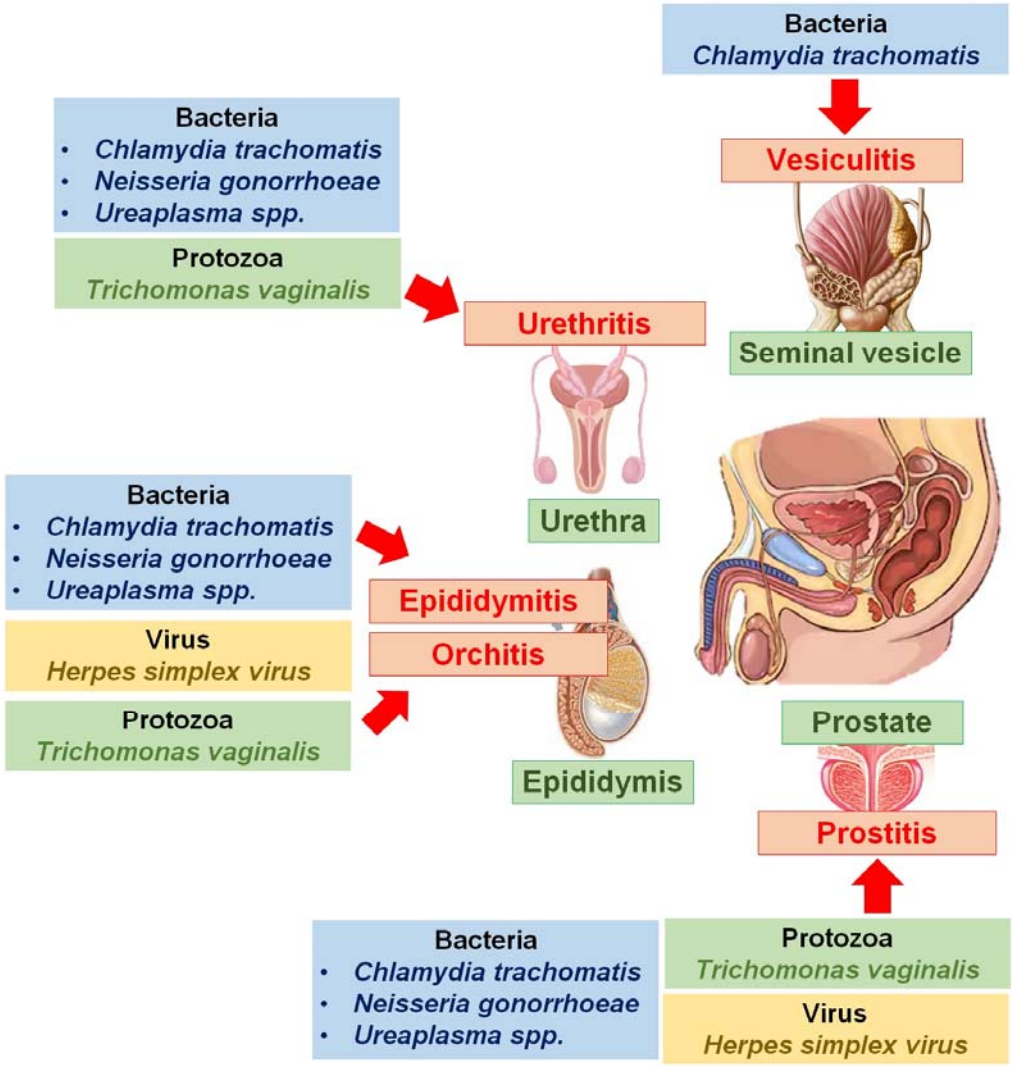


Figure 1. Various microbial pathologies of male reproductive tract.

suggests that infection frequently results in tissue damage when Chlamydia trachomatis enters the epithelial cell and thus activates IL-1. IL-1 (which consists of α and β subunits) activates polymorphonuclear WBCs and macrophages and induces IL-6, IL-8, IL-10, TNF-α, and IFN-α subsequently. In infertile men, level IL-6 in seminal plasma is higher.[67] In the semen of infertile people, MDA rates were also higher, indicating that IL-6 is involved in lipid peroxidation.[70] This sequence of cascade responses, which leads to male infertility, implicitly triggers OS. The second mechanism proposed is to induce excessive ROS through the interaction between CD14 receptor and high concentration of LPO present on the sperm membrane[17], while the third mechanism proposed indicates the production of antisperm antibodies from the invasion of macrophages, lymphocytes, plasma cells and eosinophils. The activation cascade of ILs evokes further secretory antibodies to IgA, IgM, and IgG, where IgA and IgG are typically linked to lower rates of semen parameters and pregnancy outcomes.[71,72] A meta-analysis of progression and outcome cytokine-level variations suggests that IL-1, IL-6, IL-8, IL-10, TNF-α and IFN-γ variations in hosts may potentially affect the patient's clinical outcome.[61] Early diagnostic testing and antibiotic administration (i.e., macrolides) are essential for eradication of STD, given that there are several theories.

Prostatitis

Prostatitis remains the most extensively studied inflammatory diseases amongst male urogenital diseases. In case of acute and chronic bacterial prostatitis, pathogens can influence sperm either directly (based on the pathogen's strain) or indirectly through the activation of cytokines such as IL-6, IL-8 or TNF-α[73] in the seminal tract. Elevated levels of cytokine contribute to OS, which not only affects the spermatozoa[14], but it can also potentially cause a systemic response by reducing testosterone hormone levels.[15,74] Increased IL-6, IL-8, and TNF-α levels may also impact sperm transit during ejaculation when the infection spreads to the testis.[37,75] Enhanced oxidative stress often directly affects sperm DNA and thus affects the paternal genomic contribution to the embryo.[76] Prostate infection and inflammation activate leucocytes which can increase ROS. For this reason, infections require immediate

treatment because a high amount of ROS may affect up to 35 percent of men seeking infertility therapy. This is primarily because untreated prostatitis can cause oligozoospermia, azoospermia or asthenozoospermia.[77] Untreated/undertreated infections may also cause chronic illness, which is harder to treat than acute illness. Four specific antibiotics - fluoroquinolones, tetracyclines, macrolides, and trimethoprim (alone or in combination with sulfamethoxazole) - were introduced as a treatment option in the case of bacterial prostatitis.[78] Antibiotic administration remains the foundation for the treatment of bacterial prostatitis, and numerous studies have shown that antibiotics can improve semen parameters and pregnancy rates considerably. Nevertheless, antibiotic treatment needs to be done carefully and after proper drug resistance testing, because recent attention has also been paid to multidrug resistance.[79] Combination treatment for patients is generally recommended if the first-line treatment is ineffective.[80] While most combinations are indifferent or additive, ciprofloxacin and rifampin appear to be effective against Staphylococcus aureus,[81] while fluoroquinolones chelate with cations such as aluminium, magnesium, calcium, iron and zinc. This drug interaction significantly reduces the concentrations of serum drugs available for penetration into target tissues.[81] Prostate epithelial cells can produce cell zinc which is multiple times higher than most other mammalian cells.[82] The accumulation of zinc in the prostate may prevent fluoroquinolones from achieving their optimal efficacy, despite the above description.

Male Reproductive Tract Infections and Leukocytes

Impairment of sperm functions can be triggered either by exposure to oxidants or by the reduced availability of protective antioxidant mechanisms in reproductive organs or by pathophysiological value of semen in male fertility factor.[17, 83] The main sources of these types of reactive oxygen (ROS) include immature sperm with excess residual cytoplasm and high seminal leukocytes,[17,84] which normally appear in semen, even in that of healthy fertile men without a genital tract infection.[85] While leukocytes are an essential component of the immune system, increasing numbers may not be a good sign in certain respects, or leukocyte can be considered unusual in certain parts of the body, and therefore special monitoring is needed. If a significant number of leukocytes in a semen sample are found, this is a problem as it may suggest an infection of the reproductive tract. If not treated, the testis and production of sperm may be further impaired.

Despite their critical role in the body, the leukocytes produce large amount ROS, which represents 1000 times higher production of ROS,[86] in view of immune surveillance and phagocytosis, including defective sperm.[86,87] But the number of seminal leukocytes is higher for approximately 20-30% of infertile males. It results in considerably higher ROS production in conjunction with genital infection, inflammatory reactions and cellular defense mechanisms.[12,14] The range of leucocyte types depends on the individual and mode of infection. While the largest type of leukocyte in semen is polymorphonuclear (PMN) granulocytes with 50 to 60%, macrophages and lymphocytes have 20 to 30%, and 2 to 5% respectively, respectively. While granulocytes derive mainly from the prostate and seminal vesicle, epididymis and rete testis primarily contribute to other types of white blood cells.[84,88]

Comparing the seminal levels of leucocyte in fertile and infertile men, white blood cell numbers in fertile men are usually fewer. Nonetheless, the extremely wide overlapping leucocyte ranges in fertile and infertile men make it difficult to diagnose male infertility from seminal white blood cells.[88] In its new Laboratory Manual for the Human Semen analysis, the World Health Organization has recommended[89] a clinical cut-off value of $1x10^6$/mL of semen. On the other hand, a number of studies[90,91] have questioned this value as being too high. Some authors indicated that an even greater number of leucocytes would not affect men's fertility[92] or have beneficial effects on the induction of acrosome reactions.[93] Barraud-Lange and co-workers[94] reported that Leukocyte concentrations below $1x10^6$ leukocytes/mL were associated with an increased fertilizer rate and outcomes of pregnancy. Nevertheless, recent research has not shown that high levels of leukocytes are detrimental to sperm functions, even if there is no clear limitation.[95,96]

The association between asthenozoopsermia and azoospermia with male genital tract infections and inflammation suggest deleterious leukocytospermia effects on sperm function and integrity.[97,98] In established assisted reproductive clinics, no negative consequences were observed of leucocytes on fertilization and pregnancy.[99,100] Leukocytospermia may in fact have a different effect and outcome between patients. In bacterial infections, activated leukocytes were reported to cause more harm in patients with compromise of fertility[101]. Activated leukocytes invade infected organs and release high amounts of ROS that cause infertility through oxidative stress via membrane lipid peroxidation.[75] Further studies are therefore needed to explain the effect of leucocytes on male fertility potential.

Inflammation, Cytokines on Male Reproductive Functions

During male reproductive tract inflammation, cytokines play both pleiotropic and redundant roles in mediating the immune responses. For example, the initial inflammatory responses are stimulated by the actions of IL6 and TNFα.[38] Leukocytes are infiltrated in the seminal plasma and activated by IL6 and as the number of seminal leukocytes increases, they lead to toxicity via induction of higher generation of ROS causing oxidative stress. TNFα is responsible for induction of chemokine expression and germ cell apoptosis, thereby impairing spermatogenesis and sperm development.[38,102,103] Neutrophil chemoattraction and infiltration into male reproductive tissues is also mediated by IL8.[104] Activated neutrophils initiate the process of phagocytosis. Several other essential roles of cytokines on male fertility parameters are reported. These include, restructuring of blood–testis barrier by IL1,[105] association of IL2 and IL6 with dyspermia cases as it is found to negatively correlate with testosterone production by the Leydig

cells, while it may amplify the negative feedback of testosterone over luteinizing hormone production by the anterior pituitary;[106,107] increase in IL4 in unexplained male infertility cases; negative correlation of IL17 and IL18 with sperm concentration and motility; association of IL21 with sperm auto-antibodies production;[107] and the role of interferons in unexplained male infertility cases.[108]

Leukocytes, Oxidative Stress and Male Fertility

Direct oxidation and disruption of plasma membrane lipids or DNA are the most noticeable results of OS. In addition, these functions may be over-stimulated leading to overreaction or early activation due to small amounts of ROS that lead to critical physiological events such as capacitation.

Oxidative damage to membrane lipids

In the absence of a cytoplasm with a relevant content of antioxidative defense enzymes, OS are particularly harmful to the sperm because the sperm plasma membrane contains an extraordinarily large amount of polyunsaturated fatty acids (PUFAs).[37,109] Despite this dilemma, the antioxidant defense of seminal plasma usually involves high activity of superoxide dismutase (SOD) and catalase and has been shown to have a positive correlation between the development of these enzymes and the progressive sperm motility.[110] In seminal plasma infertile patients with seminal total antioxidant capacity (TACs), which is a diagnostic criterion for male infertility, significantly lower SOD levels have been observed.[111]

PUFA is lipids that are very likely to oxidize electrons throughout a broader area of the molecule with many conjugate carbon double-bonds in the molecule. When these PUFAs are attacked by ROS, they start LPOs by degrading the PUFAs by lipid peroxyl and lipids and forming eventually genotoxins (4-hydroxy-2-alkenales, such as4-hydroxy-nonenales, resulting from ω6 fatty acids, such as DHA and 2-alkenales) as well as mutagens (Malondialdehyde).[112,113] These by-products are, in effect, a major further danger for male germ cells because they harm DNA by producing DNA adduct (primarily pyrimido[1,2-a]purine-10(3H)-one) that damage DNA indirectly[114]. Direct LPO damage to membrane lipids leads to a reduction in plasma and organelle membrane fluidity. Since sperm functions depend on membrane function, ion gradients and signal transduction mediated by receptors are compromised.[115,116] Such processes eventually result in a loss of the functionality of the sperm cells, including fertilizing capacity.[117] In this relation, it appears that the ROS generation site appears to play a role as leukocyte-derived ROS, i.e. outside the cell, affects the plasma membrane and its functions, whereas sperm-derived ROS appears to affect the integrity of sperm nuclear DNA.[23,118] Alternatively, sperm-derived ROS could also target the mitochondrial membrane potential and mitochondrial DNA integrity directly.[119,120]

Oxidative damage to DNA

Oxidative stress also causes significant direct damage to nucleic (nDNA)[121] and mitochondrial (mtDNA) DNA,[120] in addition to damaging membrane lipids with indirect consequences for DNA and genome. The strong negative association between the fragmentation of nuclear DNA with male infertility indicators as standard sperm morphology and motility is especially significant. Since cells do not only contain the nuclear DNA, but also DNA (mtDNA) in the mitochondria, which is about 100-times more susceptible to assaults causing damage and mutations than nDNA because mtDNA is not protected by histones and protamines.[122] Furthermore, mtDNA replicates more easily without proper proof reading and has only very simple repair systems for DNA55, rendering this DNA especially vulnerable for the OS.[123] In this context, St. John et al.[124] indicated a Potential risk of transmission of abnormal mtDNA for ART patients. More recently, Kao et al.[125] and Shamsi et al.[126] reported that mtDNA and mtDNA mutations, ROS, are a major etiological cause for male infertility. Furthermore, Spiropoulos et al.[127] showed that high levels of mtDNA mutations strongly correlate with poor sperm motility. Although mitochondrial DNA defects appear defective and inaccessible in oligoasthenozoospermic patients for amplification, mitochondria were functional for mobile sperm.[128] Treulen and co-workers[129] basically confirmed the idea that a potential breakdown of the mitochondrial membrane increases sperm ROS production, resulting in oxidative stress with reduced motility. Likewise, oxidative stress due to leukocytospermia will impair mitochondrial function by decreasing the capacity of the mitochondrial membrane, which would result in a vicious cycle with even more intracellular ROS output.[13]

The discussion on the position of mtDNA continues with conflicting results from other studies. Lim et al.[130] indicated that mtDNA would not undergo significant oxidative damage nor surpass that of nuclear DNA. Yet, in an analysis from a complete mtDNA sequencing of asthenozoospermic males, Pereira et al.[131] showed no evidence of the role of mitochondrial involvement in germ cell selection in the sperm motility suggests the hypothesis[132] would have to be treated very cautiously. Bandelt[133] highlighted that the false mtDNA mutation association with male infertility would have been supported by misanalysis.

Conclusion

Male infertility is caused by many different inflammatory/infectious processes.[134] It is therefore important, as each one has a unique damage mechanism and special susceptibility to antibiotics, to identifying the causative agent correctly when considering treatment. OS may serve as a common pathway by which several factors can cause male infertility. A modifiable lifestyle changes are recommended, such as cessations of tobacco / alcohol, healthy diet or antioxidant supplement with different chances of success. Antibiotic treatment remains the cornerstone of bacterial-mediated infections, on the other hand, where certain antibiotics may cause oxidative damage too. Nonetheless, a rising possibility must be considered for infections with multidrug-resistant bacterial strains. Although anti-retroviral therapy is used for the treatment of viral infection, nonnucleoside reverse transcriptase inhibitors are likely to reduce the fertility rate. To improve the efficacy of the treatment programs, further

significant steps need to be taken to understand the causes and consequences of infection mediated male fertility.

Conflict of Interest

The authors declare no conflict of interests.

REFERENCES AND NOTES

1. J. Poongothai, T. Gopenath, S. Manonayaki. Genetics of human male infertility. *Singapore Med. J.* **2009,** 50(4), 336-347.
2. A. Agarwal, A. Mulgund, A. Hamada, M.R. Chyatte. A unique view on male infertility around the globe. *Reprod. Biol. Endocrinol.* **2015,** 13(1), 37.
3. P. Sengupta, E. Borges Jr, S. Dutta, E. Krajewska-Kulak. Decline in sperm count in European men during the past 50 years. *Hum. Exp. Toxicol.* **2018,** 37(3), 247-255.
4. P. Sengupta, S. Dutta, E. Krajewska-Kulak. The disappearing sperms: analysis of reports published between 1980 and 2015. *Am. J. Men's Health* **2017,** 11(4), 1279-1304.
5. P. Sengupta, S. Dutta, M.B. Tusimin, T. İrez, E. Krajewska-Kulak. Sperm counts in Asian men: Reviewing the trend of past 50 years. *Asian Pac. J. Reprod.* **2018,** 7(2), 87-92.
6. P. Sengupta, S. Dutta. Thyroid disorders and semen quality. *Biomed. Pharmacol. J.* **2018,** 11(1), 01-10.
7. P. Sengupta. Reviewing reports of semen volume and male aging of last 33 years: From 1980 through 2013. *Asian Pac. J. Reprod.* **2015,** 4(3), 242-246.
8. A. Alahmar, S. Dutta, P. Sengupta. Thyroid hormones in male reproduction and infertility. *Asian Pac. J. Reprod.* **2019,** 8(5), 203-210.
9. P. Sengupta, S. Dutta. Metals. In: Skinner M, editor. *Encyclopedia of reproduction*: Academic Press; 2018.
10. P. Sengupta, U. Nwagha, S. Dutta, E. Krajewska-Kulak, E. Izuka. Evidence for decreasing sperm count in African population from 1965 to 2015. *Afr. Health Sci.* **2017,** 17(2), 418-427.
11. P. Sengupta, C. Cho. Pathophysiology of male infertility. In: Rizk B, Agarwal A, Sabanegh EJ, editors. *Male Infertility in Reproductive Medicine: Diagnosis and Management*: CRC Press; 2019.
12. E. Izuka, I. Menuba, P. Sengupta, S. Dutta, U. Nwagha. Antioxidants, anti-inflammatory drugs and antibiotics in the treatment of reproductive tract infections and their association with male infertility. *Chem. Biol. Lett.* **2020**, 7(2), 156-165.
13. M. Panner Selvam, P. Sengupta, A. Agarwal. Sperm DNA fragmentation and male infertility. In: Arafa Mea, editor. *Genetics of male infertility*. Switzerland: Springer Nature; 2020.
14. T. Irez, S. Bicer, S. Sahin, S. Dutta, P. Sengupta. Cytokines and adipokines in the regulation of spermatogenesis and semen quality. *Chem. Biol. Lett.* **2020**, 7(2), 131-139.
15. K. Bhattacharya, P. Sengupta, S. Dutta, I. Karkada. Obesity, systemic inflammation and male infertility. *Chem. Biol. Lett.* **2020**, 7(2), 92-98.
16. S. Dutta, A. Biswas, P. Sengupta. Obesity, endocrine disruption and male infertility. *Asian Pac. J. Reprod.* **2019,** 8(5), 195-202.
17. S. Dutta, A. Majzoub, A. Agarwal. Oxidative stress and sperm function: A systematic review on evaluation and management. *Arab J. Urol.* **2019,** 17(2), 87-97.
18. A. Agarwal, P. Sengupta, K. Leisegang. Oxidative stress in pathology of male of reproductive disorders. *Pathology: Oxidative Stress and Dietary Antioxidants*: Elsevier; 2020.
19. A. Agarwal, P. Sengupta. Oxidative Stress and its Association with Male Infertility. In: Parekattil S, Esteves S, Agarwal A, editors. *Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants*. 2 ed. Switzerland: Springer Nature; 2020.
20. S. Dutta, R. Henkel, P. Sengupta, A. Agarwal. Physiologic functions of ROS in sperm functions. In: Parekattil S, Esteves S, Agarwal A, editors. *Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants*. 2 ed. Switzerland: Springer Nature; 2020.
21. O. Theam, S. Dutta, P. Sengupta. Role of leukocytes in reproductive tract infection and male infertility. *Chem. Biol. Lett.* **2020**, 7(2), 124-130.
22. S. Dutta, P. Sengupta, M.F. Hassan, A. Biswa. Role of toll-like receptors in the reproductive tract inflammation and male infertility. *Chem. Biol. Lett.* **2020**, 7(2), 113-123.
23. A. Alahmar, A. Calogero, P. Sengupta, S. Dutta. Coenzyme Q10 improves sperm parameters, oxidative stress markers and sperm DNA fragmentation in infertile patients with idiopathic oligoasthenozoospermia. *World J. Men's Health* **2020**. doi: 10.5534/wjmh.190145.
24. F.T. Andrade-Rocha. Ureaplasma urealyticum and Mycoplasma hominis in men attending for routine semen analysis. *Urol. Int.* **2003,** 71(4), 377-381.
25. D. Taylor-Robinson. Infections due to species of Mycoplasma and Ureaplasma: an update. *Clin. Infect. Dis.* **1996,** 671-682.
26. B. Zorn, I. Virant-Klun, G. Vidmar, A. Sešek-Briški, M. Kolbezen, H. Meden-Vrtovec. Seminal elastase-inhibitor complex, a marker of genital tract inflammation, and negative IVF outcome measures: role for a silent inflammation? *Int. J. Androl.* **2004,** 27(6), 368-374.
27. P. Rowe, F. Comhaire, T. Hargreave, A. Mahmoud. Objective criteria for diagnostic categories in the standardized management of male infertility: male accessory gland infection (MAGI). *WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. World Health Organization. Cambridge University Press, Cambridge* **2000,** 52-54.
28. F. Gimenes, R.P. Souza, J.C. Bento, J.J. Teixeira, S.S. Maria-Engler, M.G. Bonini, et al. Male infertility: a public health issue caused by sexually transmitted pathogens. *Nat. Rev. Urol.* **2014,** 11(12), 672.
29. R. Gdoura, W. Kchaou, L. Ammar-Keskes, N. Chakroun, A. Sellemi, A. Znazen, et al. Assessment of Chlamydia trachomatis, Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, and Mycoplasma genitalium in semen and first void urine specimens of asymptomatic male partners of infertile couples. *J. Androl.* **2008,** 29(2), 198-206.
30. A. Wikström, J. Jensen. Mycoplasma genitalium: a common cause of persistent urethritis among men treated with doxycycline. *Sex. Trans. Infect.* **2006,** 82(4), 276-279.
31. H. Zeighami, S. Peerayeh, R. Yazdi, R. Sorouri. Prevalence of Ureaplasma urealyticum and Ureaplasma parvum in semen of infertile and healthy men. *Int. J. STD AIDS* **2009,** 20(6), 387-390.
32. G. Gallegos, B. Ramos, R. Santiso, V. Goyanes, J. Gosálvez, J.L. Fernández. Sperm DNA fragmentation in infertile men with genitourinary infection by Chlamydia trachomatis and Mycoplasma. *Fertil. Steril.* **2008,** 90(2), 328-334.
33. E.A. Abusarah, Z.M. Awwad, E. Charvalos, A.A. Shehabi. Molecular detection of potential sexually transmitted pathogens in semen and urine specimens of infertile and fertile males. *Diag. Microbiol. Infect. Dis.* **2013,** 77(4), 283-286.
34. R. Nunez-Calonge, P. Caballero, C. Redondo, F. Baquero, M. Martinez-Ferrer, M. Meseguer. Ureaplasma urealyticum reduces motility and induces membrane alterations in human spermatozoa. *Hum. Reprod.* **1998,** 13(10), 2756-2761.
35. F. Comhaire, A. Mahmoud, C. Depuydt, A. Zalata, A. Christophe. Mechanisms and effects of male genital tract infection on sperm quality and fertilizing potential: the andrologist's viewpoint. *Hum. Reprod. Update* **1999,** 5(5), 393-398.
36. B. Dahlberg. Asymptomatic bacteriospermia: Cause of infertility in men. *Urology* **1976,** 8(6), 563-566.
37. D. Sanocka, M. Kurpisz. Reactive oxygen species and sperm cells. *Reprod. Biol. Endocrinol.* **2004,** 2(1), 12.
38. E. Moretti, G. Collodel, L. Mazzi, M. Campagna, F. Iacoponi, N. Figura. Resistin, interleukin-6, tumor necrosis factor-alpha, and human semen parameters in the presence of leukocytospermia, smoking habit, and varicocele. *Fertil. Steril.* **2014,** 102(2), 354-360.
39. J. Ramirez, A. Carreras, C. Mendoza. Sperm plasma membrane integrity in fertile and infertile men. *Andrologia* **1992**,24(3), 141-144.
40. F. Galdiero, L. Sommese, F. Gorga, E. Galdiero, A. Rizzo, M. Ajello. Toxic effect on human spermatozoa by Chlamydia trachomatis purified lipopolysaccharide. *FEMS Microbiol. Lett.* **1994,** 115(2-3), 197-200.

41. R. Boguen, F. Treulen, P. Uribe, J.V. Villegas. Ability of Escherichia coli to produce hemolysis leads to a greater pathogenic effect on human sperm. *Fertil. Steril.* **2015,** 103(5), 1155-1161.
42. A. Garolla, D. Pizzol, A. Bertoldo, M. Menegazzo, L. Barzon, C. Foresta. Sperm viral infection and male infertility: focus on HBV, HCV, HIV, HPV, HSV, HCMV, and AAV. *J. Reprod. Immunol.* **2013,** 100(1), 20-29.
43. A. Garolla, M. Torino, B. Sartini, I. Cosci, C. Patassini, U. Carraro, et al. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. *Hum. Reprod.* **2013,** 28(4), 877-885.
44. S. Kehl, M. Weigel, D. Müller, M. Gentili, A. Hornemann, M. Sütterlin. HIV-infection and modern antiretroviral therapy impair sperm quality. *Arch. Gynecol. Obs.* **2011,** 284(1), 229-233.
45. J. Singh, B.S. Chhikara. Comparative global epidemiology of HIV infections and status of current progress in treatment. *Chem. Biol. Lett.* **2014**, 1 (1), 14–32.
46. C. Frapsauce, S. Grabar, M. Leruez-Ville, O. Launay, P. Sogni, V. Gayet, et al. Impaired sperm motility in HIV-infected men: an unexpected adverse effect of efavirenz? *Hum. Reprod.* **2015,** 30(8), 1797-1806.
47. S. La Vignera, E. Vicari, R. Condorelli, R. D'agata, A. Calogero. Male accessory gland infection and sperm parameters. *Int. J. Androl.* **2011,** 34(5pt2), e330-e347.
48. Y.H. Zhou, H.X. Ma, X.X. Shi, Y. Liu. Ureaplasma spp. in male infertility and its relationship with semen quality and seminal plasma components. *J. Microbiol. Immunol. Infect.* **2018,** 51(6), 778-783.
49. X. Kang, Q. Xie, X. Zhou, F. Li, J. Huang, D. Liu, et al. Effects of hepatitis B virus S protein exposure on sperm membrane integrity and functions. *PLoS One* **2012,** 7(3).
50. L. Qian, Q. Li, H. Li. Effect of hepatitis B virus infection on sperm quality and oxidative stress state of the semen of infertile males. *Am. J. Reprod. Immunol.* **2016,** 76(3), 183-185.
51. R. Sacks-Davis, E. Mcbryde, J. Grebely, M. Hellard, P. Vickerman. Many hepatitis C reinfections that spontaneously clear may be undetected: Markov-chain Monte Carlo analysis of observational study data. *J. Royal Soc. Int.* **2015,** 12(104), 20141197.
52. L. Benova, Y.A. Mohamoud, C. Calvert, L.J. Abu-Raddad. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin. Infect. Dis.* **2014,** 59(6), 765-773.
53. K. Machida, K.T.-H. Cheng, C.-K. Lai, K.-S. Jeng, V.M.-H. Sung, M.M. Lai. Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. *J. Virol.* **2006,** 80(14), 7199-7207.
54. S. La Vignera, R. Condorelli, E. Vicari, R. D'agata, A. Calogero. High frequency of sexual dysfunction in patients with male accessory gland infections. *Andrologia* **2012,** 44, 438-446.
55. S. Mazzoli, T. Cai, P. Addonisio, A. Bechi, N. Mondaini, R. Bartoletti. Chlamydia trachomatis infection is related to poor semen quality in young prostatitis patients. *Eur. Urol.* **2010,** 57(4), 708-714.
56. V. Ouzounova-Raykova, S. Rangelov, I. Ouzounova, I. Mitov. Detection of Chlamydia trachomatis, Ureaplasma urealyticum and Mycoplasma hominis in infertile Bulgarian men with multiplex real-time polymerase chain reaction. *Apmis* **2015,** 123(7), 586-588.
57. J. Jarecki-Black, W. Lushbaugh, L. Golosov, A. Glassman. Trichomonas vaginalis: preliminary characterization of a sperm motility inhibiting factor. *Annals Clin. Lab. Sci.* **1988,** 18(6), 484-489.
58. A. Azenabor, A.O. Ekun, O. Akinloye. Impact of inflammation on male reproductive tract. *J. Reprod. Infert.* **2015,** 16(3), 123.
59. A. Château, H.S. Seifert. Neisseria gonorrhoeae survives within and modulates apoptosis and inflammatory cytokine production of human macrophages. *Cell. Microbiol.* **2016,** 18(4), 546-560.
60. N. Mavrogiorgos, S. Mekasha, Y. Yang, M.A. Kelliher, R.R. Ingalls. Activation of NOD receptors by Neisseria gonorrhoeae modulates the innate immune response. *Innate Immun.* **2014,** 20(4), 377-389.
61. M. Singer, S. Ouburg. Effect of cytokine level variations in individuals on the progression and outcome of bacterial urogenital infections—a meta-analysis. *Path. Dis.* **2016,** 74(2).
62. P. Sengupta, K. Bhattacharya, S. Dutta. Leptin and male reproduction. *Asian Pac. J. Reprod.* **2019,** 8(5), 220-226.
63. P. Sengupta, S. Dutta, M. Tusimin, I.R. Karkada. Orexins and male reproduction. *Asian Pac. J. Reprod.* **2019,** 8(5), 233-238.
64. T. İrez, I.R. Karkada, S. Dutta, P. Sengupta. Obestatin in male reproduction and infertility. *Asian Pac. J. Reprod.* **2019,** 8(5), 239-243.
65. S. Dutta, A. Biswas, P. Sengupta, U. Nwagha. Ghrelin and male reproduction. *Asian Pac. J. Reprod.* **2019,** 8(5), 227-232.
66. S. Dutta, P. Sengupta, A. Biswas. Adiponectin in male reproduction and infertility. *Asian Pac. J. Reprod.* **2019,** 8(5), 244-250.
67. I. Kocak, C. Yenisey, M. Dündar, P. Okyay, M. Serter. Relationship between seminal plasma interleukin-6 and tumor necrosis factor α levels with semen parameters in fertile and infertile men. *Urol. Res.* **2002,** 30(4), 263-267.
68. L. Newman, J. Rowley, S. Vander Hoorn, N.S. Wijesooriya, M. Unemo, N. Low, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PloS One* **2015,** 10(12).
69. M. Reichart, I. Kahane, B. Bartoov. In vivo and in vitro impairment of human and ram sperm nuclear chromatin integrity by sexually transmitted Ureaplasma urealyticum infection. *Biol. Reprod.* **2000,** 63(4), 1041-1048.
70. M. Camejo, A. Segnini, F. Proverbio. Interleukin-6 (IL-6) in seminal plasma of infertile men, and lipid peroxidation of their sperm. *Arch. Androl.* **2001,** 47(2), 97-101.
71. S. Dutta, P. Sengupta, N. Haque. Reproductive immunomodulatory functions of B cells in pregnancy: B cells are critical players in pregnancy that fine-tune immune tolerance and response, by crosstalks with gestational hormones. *Int. Rev. Immunol.* **2019,** 1-14.
72. S. Dutta, P. Sengupta. Functions of follicular and marginal zone B cells in pregnancy. *Asian Pac. J. Reprod.* **2018,** 7(4), 191-192.
73. S. Alshahrani, J. Mcgill, A. Agarwal. Prostatitis and male infertility. *J. Reprod. Immunol.* **2013,** 100(1), 30-36.
74. T. Bhattarai, P. Chaudhuri, K. Bhattacharya, P. Sengupta. Effect of progesterone supplementation on post-coital unilaterally ovariectomized superovulated mice in relation to implantation and pregnancy. *Asian J. Pharm. Clin. Res.* **2014,** 7(1), 29-31.
75. P. Martínez, F. Proverbio, M.I. Camejo. Sperm lipid peroxidation and pro-inflammatory cytokines. *Asian J. Androl.* **2007,** 9(1), 102-107.
76. K. Tremellen. Oxidative stress and male infertility—a clinical perspective. *Hum. Reprod. Update* **2008,** 14(3), 243-258.
77. H.C. Schuppe, A. Meinhardt, J. Allam, M. Bergmann, W. Weidner, G. Haidl. Chronic orchitis: a neglected cause of male infertility? *Andrologia* **2008,** 40(2), 84-91.
78. B.A. Lipsky, I. Byren, C.T. Hoey. Treatment of bacterial prostatitis. *Clin. Infect. Dis.* **2010,** 50(12), 1641-1652.
79. K. Krupp, P. Madhivanan. Antibiotic resistance in prevalent bacterial and protozoan sexually transmitted infections. *Indian J. Sex. Transmitt. Dis. AIDS* **2015,** 36(1), 3.
80. V. Magri, A. Trinchieri, G. Pozzi, A. Restelli, M.C. Garlaschi, E. Torresani, et al. Efficacy of repeated cycles of combination therapy for the eradication of infecting organisms in chronic bacterial prostatitis. *Int. J. Antimicrob. Agents* **2007,** 29(5), 549-556.
81. C.M. Oliphant, G. Green. Quinolones: a comprehensive review. *Am. Fam. Phys.* **2002,** 65(3), 455.
82. L. Costello, P. Feng, B. Milon, M. Tan, R. Franklin. Role of zinc in the pathogenesis and treatment of prostate cancer: critical issues to resolve. *Prost. Cancer Prost. Dis.* **2004,** 7(2), 111-117.
83. K. Bhattacharya, P. Sengupta, S. Dutta. Role of melatonin in male reproduction. *Asian Pac. J. Reprod.* **2019,** 8(5), 211-219.
84. P. Sengupta. Recent trends in male reproductive health problems. *Asian J. Pharm. Clin. Res.* **2014,** 7(2), 1-5.
85. E.E. Wallach, H. Wolff. The biologic significance of white blood cells in semen. *Fertil. Steril.* **1995,** 63(6), 1143-1157.
86. W. Ford, K. Whittington, A. Williams. Reactive oxygen species in human sperm suspensions: production by leukocytes and the generation

of NADPH to protect sperm against their effects. *Int. J. Androl.* **1997,** 20, 44-49.
87. M. Plante, E. De Lamirande, C. Gagnon. Reactive oxygen species released by activated neutrophils, but not by deficient spermatozoa, are sufficient to affect normal sperm motility. *Fertil. Steril.* **1994,** 62(2), 387-393.
88. E. De Lamirande, C. Gagnon. Capacitation-associated production of superoxide anion by human spermatozoa. *Free Rad. Biol. Med.* **1995,** 18(3), 487-495.
89. World Health Organization. WHO laboratory manual for the examination and processing of human semen. **2010**.
90. R.K. Sharma, F.F. Pasqualotto, D.R. Nelson, A. Agarwal. Relationship between seminal white blood cell counts and oxidative stress in men treated at an infertility clinic. *J. Androl.* **2001,** 22(4), 575-583.
91. M. Punab, K. Lõivukene, K. Kermes, R. Mändar. The limit of leucocytospermia from the microbiological viewpoint. *Andrologia* **2003,** 35(5), 271-278.
92. E.H. Yanushpolsky, J.A. Politch, J.A. Hill, D.J. Anderson. Is leukocytospermia clinically relevant? *Fertil. Steril.* **1996,** 66(5), 822-825.
93. S. Kaleli, F. Öçer, T. Irez, E. Budak, M.F. Aksu. Does leukocytospermia associate with poor semen parameters and sperm functions in male infertility?: The role of different seminal leukocyte concentrations. *Eur. J. Obs. Gyn. Reprod. Biol.* **2000,** 89(2), 185-191.
94. V. Barraud-Lange, J.-C. Pont, A. Ziyyat, K. Pocate, C. Sifer, I. Cedrin-Durnerin, et al. Seminal leukocytes are Good Samaritans for spermatozoa. *Fertil. Steril.* **2011,** 96(6), 1315-1319.
95. J.S. Sandoval, D. Raburn, S. Muasher. Leukocytospermia: overview of diagnosis, implications, and management of a controversial finding. *Mid. East Fertil. Soc. J.* **2013,** 18(3), 129-134.
96. M. Fraczek, M. Hryhorowicz, K. Gill, M. Zarzycka, D. Gaczarzewicz, P. Jedrzejczak, et al. The effect of bacteriospermia and leukocytospermia on conventional and nonconventional semen parameters in healthy young normozoospermic males. *J. Reprod. Immunol.* **2016,** 118, 18-27.
97. G. Dohle, G. Colpi, T. Hargreave, G. Papp, A. Jungwirth, W. Weidner, et al. EAU guidelines on male infertility. *Eur. Urol.* **2005,** 48(5), 703-711.
98. J.E. Lackner, R. Herwig, J. Schmidbauer, G. Schatzl, C. Kratzik, M. Marberger. Correlation of leukocytospermia with clinical infection and the positive effect of antiinflammatory treatment on semen quality. *Fertil. Steril.* **2006,** 86(3), 601-605.
99. M. Cavagna, J.B.A. Oliveira, C.G. Petersen, A.L. Mauri, L.F. Silva, F.C. Massaro, et al. The influence of leukocytospermia on the outcomes of assisted reproductive technology. *Reprod. Biol. Endocrinol.* **2012,** 10(1), 44.
100. G. Ricci, M. Granzotto, S. Luppi, E. Giolo, M. Martinelli, G. Zito, et al. Effect of seminal leukocytes on in vitro fertilization and intracytoplasmic sperm injection outcomes. *Fertil. Steril.* **2015,** 104(1), 87-93.
101. E. Moretti, S. Capitani, N. Figura, A. Pammolli, M.G. Federico, V. Giannerini, et al. The presence of bacteria species in semen and sperm quality. *J. Assist. Reprod. Genet.* **2009,** 26(1), 47.
102. Z. Kopa, J. Wenzel, G. Papp, G. Haidl. Role of granulocyte elastase and interleukin-6 in the diagnosis of male genital tract inflammation. *Andrologia* **2005,** 37(5), 188-194.
103. P. Sengupta, M. Arafa, H. Elbardisi. Hormonal regulation of spermatogenesis. In: Singh R, editor. *Molecular signaling in spermatogeneis and male infertility*. New Delhi, India: CRC Press; 2019.
104. P. Saxena, R. Soni, V. Randhawa, N. Singh. Can Seminal IL-8 Level Be Used as a Marker of Leukocytospermia and Does It Have Any Correlation with Semen Parameters in Infertile Couples? *J. Obs. Gyn. India* **2019,** 69(5), 451-456.
105. M. Fijak, S. Bhushan, A. Meinhardt. The immune privilege of the testis. *Immune Infertility*: Springer; 2017. p. 97-107.
106. V. Syriou, D. Papanikolaou, A. Kozyraki, D.G. Goulis. Cytokines and male infertility. *Eur. Cytokine Network* **2018,** 29(3), 73-82.
107. L.-F. An, X.-H. Zhang, X.-T. Sun, L.-H. Zhao, S. Li, W.-H. Wang. Unexplained infertility patients have increased serum IL-2, IL-4, IL-6, IL-8, IL-21, TNFα, IFNγ and increased Tfh/CD4 T cell ratio: Increased Tfh and IL-21 strongly correlate with presence of autoantibodies. *Immunol. Invest.* **2015,** 44(2), 164-173.
108. M. Munoz, S. Witkin. Autoimmunity to spermatozoa, asymptomatic Chlamydia trachomatis genital tract infection and gd T lymphocytes in seminal fluid from the male partners of couples with unexplained infertility. *Hum. Reprod.* **1995,** 10(5), 1070-1074.
109. A.A. Zalata, A.B. Christophe, C.E. Depuydt, F. Schoonjans, F.H. Comhaire. The fatty acid composition of phospholipids of spermatozoa from infertile patients. *Mol. Hum. Reprod.* **1998,** 4(2), 111-118.
110. B. Macanovic, M. Vucetic, A. Jankovic, A. Stancic, B. Buzadzic, E. Garalejic, et al. Correlation between sperm parameters and protein expression of antioxidative defense enzymes in seminal plasma: a pilot study. *Dis. Markers* **2015,** 2015.
111. M. Murawski, J. Saczko, A. Marcinkowska, A. Chwiłkowska, M. Gryboś, T. Banaś. Evaluation of superoxide dismutase activity and its impact on semen quality parameters of infertile men. *Folia Histochem. Cytobiol.* **2007,** 45(I), 123-126.
112. H. Esterbauer. Cytotoxicity and genotoxicity of lipid-oxidation products. *Am. J. Clin. Nutr.* **1993,** 57(5), 779S-786S.
113. W. Łuczaj, E. Skrzydlewska. DNA damage caused by lipid peroxidation products. *Cell. Mol. Biol. Lett.* **2003,** 8(2), 391-413.
114. L.J. Marnett. Lipid peroxidation—DNA damage by malondialdehyde. *Mut. Res.* **1999,** 424(1-2), 83-95.
115. R. Walczak–Jedrzejowska, J.K. Wolski, J. Slowikowska–Hilczer. The role of oxidative stress and antioxidants in male fertility. *Centr. Eur. J. Urol.* **2013,** 66(1), 60.
116. S.C. Sikka. Relative impact of oxidative stress on male reproductive function. *Curr. Med. Chem.* **2001,** 8(7), 851-862.
117. A. Carpino, L. Siciliano, M. Petroni, C. De Stefano, S. Aquila, S. Ando, et al. Low seminal zinc bound to high molecular weight proteins in asthenozoospermic patients: evidence of increased sperm zinc content in oligoasthenozoospermic patients. *Hum. Reprod.* **1998,** 13(1), 111-114.
118. R. Henkel, E. Kierspel, T. Stalf, C. Mehnert, R. Menkveld, H.-R. Tinneberg, et al. Effect of reactive oxygen species produced by spermatozoa and leukocytes on sperm functions in non-leukocytospermic patients. *Fertil. Steril.* **2005,** 83(3), 635-642.
119. S. Venkatesh, M. Deecaraman, R. Kumar, M. Shamsi, R. Dada. Role of reactive oxygen species in the pathogenesis of mitochondrial DNA (mtDNA) mutations in male infertility. *Indian J. Med. Res.* **2009,** 129(2).
120. A.P. Sousa, A. Amaral, M. Baptista, R. Tavares, P.C. Campo, P.C. Peregrín, et al. Not all sperm are equal: functional mitochondria characterize a subpopulation of human sperm with better fertilization potential. *PloS One* **2011,** 6(3), e18112.
121. E. Seli, D.K. Gardner, W.B. Schoolcraft, O. Moffatt, D. Sakkas. Extent of nuclear DNA damage in ejaculated spermatozoa impacts on blastocyst development after in vitro fertilization. *Fertil. Steril.* **2004,** 82(2), 378-383.
122. G. Pesole, C. Gissi, A. De Chirico, C. Saccone. Nucleotide substitution rate of mammalian mitochondrial genomes. *J. Mol. Evol.* **1999,** 48(4), 427-434.
123. D.L. Croteau, R.H. Stierum, V.A. Bohr. Mitochondrial DNA repair pathways. *Mut. Res.* **1999,** 434(3), 137-148.
124. J.C. St John, R. Lloyd, S. El Shourbagy. The potential risks of abnormal transmission of mtDNA through assisted reproductive technologies. *Reprod. Biomed. Online* **2004,** 8(1), 34-44.
125. S.-H. Kao, H.-T. Chao, H.-W. Liu, T.-L. Liao, Y.-H. Wei. Sperm mitochondrial DNA depletion in men with asthenospermia. *Fertil. Steril.* **2004,** 82(1), 66-73.

126.M.B. Shamsi, R. Kumar, A. Bhatt, R. Bamezai, R. Kumar, N.P. Gupta, et al. Mitochondrial DNA mutations in etiopathogenesis of male infertility. *Indian J. Urol.* **2008,** 24(2), 150.
127.J. Spiropoulos, D.M. Turnbull, P.F. Chinnery. Can mitochondrial DNA mutations cause sperm dysfunction? *MHR Basic Sci. Reprod. Med.* **2002,** 8(8), 719-721.
128.E. Carra, D. Sangiorgi, F. Gattuccio, A.M. Rinaldi. Male infertility and mitochondrial DNA. *Biochem. Biophys. Res. Comm.* **2004,** 322(1), 333-339.
129.F. Treulen, P. Uribe, R. Boguen, J. Villegas. Mitochondrial outer membrane permeabilization increases reactive oxygen species production and decreases mean sperm velocity but is not associated with DNA fragmentation in human sperm. *MHR Basic Sci. Reprod. Med.* **2015,** 22(2), 83-92.
130.K.S. Lim, K. Jeyaseelan, M. Whiteman, A. Jenner, B. Halliwell. Oxidative damage in mitochondrial DNA is not extensive. *Annals NY Acad. Sci.* **2005,** 1042(1), 210-220.
131.L. Pereira, J. Gonçalves, R. Franco-Duarte, J. Silva, T. Rocha, C. Arnold, et al. No evidence for an mtDNA role in sperm motility: data from complete sequencing of asthenozoospermic males. *Mol. Biol. Evol.* **2007,** 24(3), 868-874.
132.F.L. Moore, R.A. Reijo-Pera. Male sperm motility dictated by mother's mtDNA. *Am. J. Hum. Genet.* **2000,** 67(3), 543-548.
133.H.J. Bandelt. Misanalysis gave false association of mtDNA mutations with infertility. *Int. J. Androl.* **2008,** 31(4), 450-453.
134. S. Dutta, P. Sengupta, B.S. Chhikara. Reproductive Inflammatory Mediators and Male Infertility. *Chem. Biol. Lett.* **2020**, 7 (2l), 73–74.

AUTHORS BIOGRAPHIES

Dr. Pallav Sengupta, is a Faculty in the School of Medicine, MAHSA University, Malaysia and had served as the Head of Physiology Unit in the Faculty of Medicine, Lincoln University College, Malaysia. He has obtained his PhD in Reproductive Endocrinology from the University of Calcutta, India. His key research interests include Infertility and Reproductive Medicine. His research has yielded a substantial number of publications including several research articles, books and book chapters.

Dr. Sulagna Dutta, is a Faculty and the Research Coordinator in the School of Dentistry, MAHSA University, Malaysia. Following her Masters in Physiology, Dr. Dutta has earned her PhD in Immunology from the University of Calcutta, India. Her research interests are in the realms of Immunology and Reproductive Physiology. She has published numerous research articles and book chapters.

Dr. Ahmed T Alahmar is a lecturer at the College of Medicine, University of Babylon, Iraq. He obtained MBChB (Hons.) in Medicine and MSc. (Hons.) in Medical Physiology from the University of Babylon, Iraq. He also received research training at the University of Manchester, UK. Dr. Alahmars research interests include male infertility research and the role of oxidative stress and sperm DNA damage in male infertility. Dr. Alahmar published many research articles in peer-reviewed international journals and he is also a reviewer for international journals indexed in Web of Science, Scopus and PubMed.

Professor Dr. Urban John Arnold D'Souza is a Professor of Biomedical Sciences & Therapeutics Department at the Faculty of Medicine & Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu Sabah, Malaysia. He has 30 years of teaching and research experience in Medical Schools. He has published about a hundred articles in different areas, especially in Reproductive Physiology. He has supervised around 12 Ph.D. scholars and currently working on areas of Medical Education, leptin-ghrelin-obesity, Emotional Quotient – Academic excellence. He is a Fellow of Royal Society of Biologists and former Head of the Department in the current Faculty.