Review Article

Seminal Plasma Biochemical Markers and Microbial Infections: Diagnostic and Pathophysiological Insights into Male Infertility

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ABSTRACT

Male infertility is a multifactorial condition, with an increasing body of evidence highlighting the pivotal role of seminal plasma biochemical markers and microbial infections in its pathogenesis and diagnosis. Seminal plasma, a complex fluid enriched with proteins, enzymes, antioxidants, and metabolites, reflects the functional status of the male reproductive tract. Alterations in its biochemical composition, such as decreased antioxidant capacity, disrupted energy metabolism, and elevated inflammatory mediators, are frequently associated with impaired sperm function. Concurrently, microbial infections, including those caused by *Chlamydia trachomatis* and *Escherichia coli*, can adversely affect seminal parameters through direct sperm damage, oxidative stress, and inflammatory responses. Emerging evidence suggests intricate interactions between infections and the biochemical milieu in seminal plasma, which may exacerbate sperm dysfunction and compromise fertility. This review synthesizes current knowledge on key seminal plasma biomarkers and their diagnostic utility and elucidates the pathophysiological mechanisms linking microbial infections to male infertility. Understanding these interconnected pathways offers novel insights into male reproductive health and may facilitate the development of more targeted diagnostic and treatment strategies in the context of infertility.

Keywords: Seminal plasma; Male infertility; Biochemical markers; Microbial infections

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Introduction

Infertility affects over 20% of couples worldwide and has emerged as a critical health concern in recent decades. Studies indicate that approximately 50% of infertility cases are due to male-related factors. In men, a wide range of factors can contribute to infertility, including lifestyle habits, hormonal imbalances, ejaculation disorders, varicocele, excessive alcohol consumption, hypogonadism, sperm dysfunction, infections in the genitourinary tract, and genetic abnormalities (1). A growing body of evidence highlights the role of microbial infections, particularly bacterial and viral infections of the male urogenital tract, in contributing to subfertility. In fact, up to 35% of male infertility cases are linked to infections of the genitourinary system (2). These infections can damage reproductive cells and impair their function. They are also associated with an increase in leukocytes within the seminal plasma, a condition known as leukocytospermia, often accompanied by bacteriospermia. Such infections may interfere with spermatogenesis, compromise sperm function, and disrupt the overall reproductive system (Figure. 1) (3). Male genital tract infections are often difficult to detect, frequently presenting without symptoms. This asymptomatic nature can lead to the transmission of pathogens to sexual partners, resulting in infertility, pregnancy loss, and potential health complications in offspring (4). With the growing global concern of antibiotic resistance among urogenital pathogens, accurate diagnosis and effective treatment are essential for managing these infections (4). This review explores recent studies examining the effects of specific bacterial species, including *Escherichia coli*, *Bacteroides ureolyticus*, *Chlamydia trachomatis*, *Pseudomonas aeruginosa*, and *Mycoplasma hominis*, on sperm quality. We also discuss the diagnostic potential of seminal plasma composition as a biomarker for male infertility.

Importance of the seminal plasma components for male fertility

In recent decades, the progressive decline in human fertility has gained increasing global attention, emerging as a critical medical and societal concern (5). Despite extensive research, the majority of the underlying causes and molecular pathways of male infertility remain poorly understood. Therefore, it is essential to identify key elements influencing male fertility, investigate the

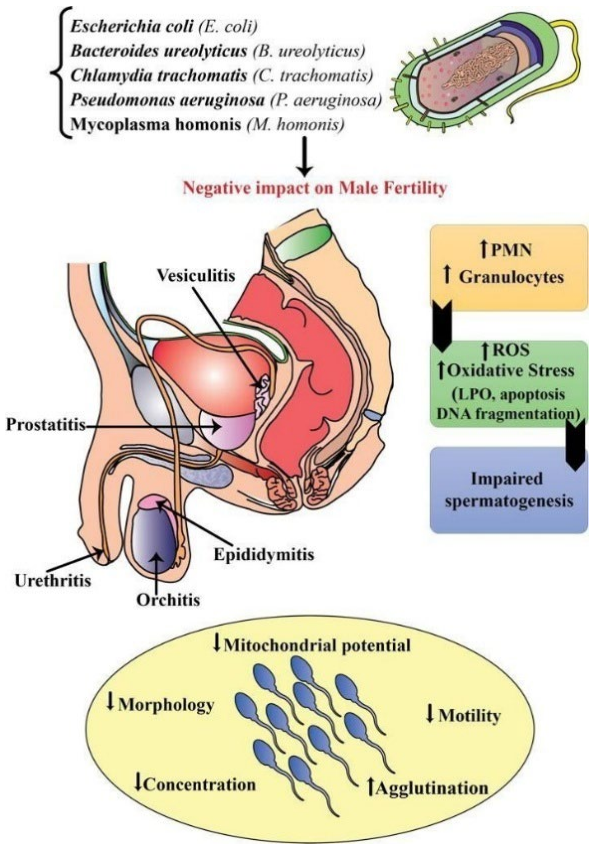

Figure 1. Bacterial infections negatively affect male infertility. The presence of certain bacteria can indicate an infection with harmful consequences. Some pathogens can cause inflammation and oxidative stress, which can affect spermatogenesis and reduce sperm quality.

associated regulatory mechanisms, discover reliable diagnostic biomarkers, and ultimately develop effective therapeutic strategies (6).

In addition to the testes, male reproductive function relies heavily on the accessory sex glands, namely the prostate, seminal vesicles, and bulbourethral glands. These glands secrete seminal plasma (SP), a vital biological fluid that supports the transport and function of sperm from ejaculation through to fertilization. Seminal plasma is composed of a diverse array of molecular components, including fructose, proteins, lipids, cell-free nucleic acids (such as lncRNAs, DNA, and microRNAs), various metabolites, and ions. These components provide the energy necessary for sperm motility and metabolism. Moreover, they play a regulatory role in sperm function by orchestrating key molecular events such as sperm maturation in the epididymis and capacitation during the journey through the female reproductive tract (7).

Protein components of seminal plasma

Human normal seminal plasma (SP) mainly contains a variety of peptides and tissue-specific proteins that bind directly to spermatozoa and contribute to sperm maturity and interplay with the female genital tract. Seminal plasma proteins are primarily derived from the prostate and seminal vesicles, which produce approximately 20–30% and 65–75% of semen volume, respectively. Also, a small fraction is produced by the epididymis, testes, and periurethral and bulbourethral glands. However, the total concentration of protein is variable, largely based on the detection method, with an average range of 40 to 60 mg/mL (8–10) (Table 1). Serpin family A member 1 (SERPINA1) is an acute phase protein responsible for inhibiting proteases involved in inflammatory responses. During inflammation, its expression level increases in plasma (11). Fibronectin-1 (FN1) is a multifunctional glycoprotein found in SP and is involved in seminal gel formation after ejaculation and stimulates sperm capacity (12). Some reports have shown the overexpression of FN1 in patients with azoospermia (13).

Cell-free nucleic acids of SP

Cell-free nucleic acids of SP primarily comprise cell-free RNAs (cfRNAs) and cell-free DNAs (cfDNAs), consisting of messenger RNAs (mRNAs), microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), as well as long non-coding RNAs (lncRNAs). The content of seminal cfDNA with low molecular weight has a significant correlation with the fast development, curvilinear velocity, capacity index, and morphology of sperm. Cell-free DNA (cfDNA) originating from the testes carries valuable epigenetic information and has emerged as a promising non-invasive biomarker for identifying abnormalities and disorders in spermatogenesis (10). On the other hand, microRNAs (miRNAs) play critical roles in regulating a wide range of cellular signaling pathways, including stress responses, metabolic processes, apoptosis, cell differentiation, tumor metastasis, and notably, spermatogenesis (14). Some specific miRNA alterations in seminal plasma are associated with infertility in men and their spermatogenic disorders, which could be adopted as diagnostic markers for detection of infertility in men (Table 1). A study showed that the mean concentration of cfDNA in normozoospermic semen was determined to be 1.3 ± 0.6 µg/mL, while a greater concentration was detectable in azoospermia, with values of 2.5 ± 1.4 µg/mL (15). In addition, it is possible to detect testis-specific methylated gene promoters (ACRBP, CCNA1, DMRT1, HSF1, and CIB1) from seminal cfDNA that are positively associated with methylation in testicular DNA (16).

Hormones in seminal plasma

Changes in the SP hormonal profiles showed correlations with abnormalities of the sperm. Lower levels of dihydrotestosterone and seminal testosterone

Table 1. The functions of seminal plasma composition in patients with male infertility

Sp Composition	Sample Type	Significance	Function
PIGR	Bilateral varicocele	Increase	Inflammatory Response (67)
PRDX1	Bilateral varicocele	Increase	Responsible to Rox and oxidative stress (68)
LDHC	asthenozoospermia	Decrease	Be required for normal infertility (69)
FASN	Bilateral varicocele	Increase	associated with the molecular pathways related to DNA damage and vital for its regulation (70)
miR 192a	Varicocele	Increase	Apoptosis of GC-2 cell via caspase3 activation (71)
miR122	varicocele and oligozoospermia	Increase	associated with OS & apoptosis markers (BCL2 & BAX) (72)
AMH	Oligozoospermia	Decrease	Involved in sperm production
B-HCG	infertile patient	Decrease	Regulation of testosterone secretion
Relaxin	infertile patient	Decrease	Maintains lower levels of apoptosis & greater mitochondrial activities (73).

Table 2. Effects of bacterial strains on seminal tract infections both in vivo and in vitro

Bacterial stain	Studies	Mechanism proposed
Escherichia coli	In vitro	Adhere to spermatozoa and lead to sperm agglutination and considerable changes in spermatozoa (74)
Bacteroides ureolyticus	In vitro	Impair the functions and structures of the sperms via reducing motility and injuring the sperms' membranes (75)
Chlamydia trachomatis	In vivo	Pneumonitis biovar (MOPN) Decrease sperm motility, viability and normal morphology (76)
Pseudomonas aeruginosa	In vivo	Cell free fetal dna impaired motility of the sperms, viability, & Mg-dependent ATPase activities, premature acrosome & and induced morphological alteration(decapitation) (77)
Mycoplasma homonis	In vivo/ In vitro	Reduced inducibility of human sperms' acrosome reaction (78)

were also observed in cases with low sperm concentration and motility compared to men with normospermia. A seminal plasma proteins study in patients with hypogonadotrophic hypogonadism showed that the levels of 11 proteins, primarily involved in protein binding and hydrolysis activities, were decreased, while concentrations of 6 proteins were restored following the Testosterone Replacement Therapy (TRT) stage (17). One study showed a significant reduction in SP concentrations of prostatic acid phosphatase, fructose, lactoferrin, zinc (Zn), and prostate-specific antigen after TRT (18). Furthermore, one injection of testosterone enanthate (TE) resulted in increased concentrations of sialic acid and fructose and higher activity of the ornithine decarboxylase enzyme in oligospermic males (19).

In addition to testosterone (T), several other hormones including human chorionic gonadotropin (hCG), estradiol, anti-Müllerian hormone (AMH), and relaxin are also present in SP. Among these, estradiol levels have been found to be significantly elevated in infertile men (20). Notably, estradiol concentrations are higher in individuals with obstructive azoospermia (OA) compared to those with non-obstructive azoospermia (NOA) and men with normal sperm parameters (normospermic) (21). It should be noted that AMH is one of the dimeric glycoproteins generated by Sertoli cells from the beta superfamily of transforming growth factors (TGF). Therefore, AMH in semen could not be identified in every OA patient because of its source. Also, the total AMH content (pmol/ejaculate) in SP is positively correlated with sperm count and sperm concentration (22). For human chorionic gonadotropin (hCG), free beta subunit concentrations have been shown to be lower in infertile men compared to the healthy control group and correlate with sperm motility and count (23).

Relaxin has been proposed as one of the reproductive hormones produced by the ovaries and placenta. Relaxin contributes to pregnancy and labor in women and is found at a concentration of approximately 50 ng/mL in seminal plasma, originally produced by prostate tissue (24). This hormone has a positive influence on the fertilization function of sperm. Nonetheless, researchers disagree about the influence of this hormone on sperm motility. Some studies have shown effects of relaxin on the motility of human sperm (25, 26), whereas others could not provide conclusive findings on this issue (27, 28).

Immune factors in seminal plasma

Sperm cells are recognized as both autoantigens and alloantigens, and the immune system plays a crucial role in male and female fertility. Cytokines are part of the autocrine/paracrine network in the male reproductive system and have a critical role in spermatogenesis and testicular function. All types of cells in the human reproductive system can produce cytokines, and in cases of abnormality, elevated levels of cytokines can affect reproductive system function. In this regard, lower IL-6 levels in severe and mild oligozoospermia and higher IL-8 and IL-10 concentrations in asthenospermia have been reported. Moreover, one study reported that the IL-11 level in the seminal fluid of the infertility group of men is positively correlated with motility, viability, normal sperm morphology, and survival rate, whereas IL-18 and IL-17 concentrations showed negative correlations (29, 30).

Some harmful factors such as infection, obstruction, and injury cause the opening of the blood barriers (BB) of the testis, resulting in contact of spermatids, sperm, and spermatocytes with the body's immune system and subsequently an autoimmune reaction and production of diverse kinds of testicular anti-sperm antibodies (ASA). Autoimmune reaction to the sperm, followed by production of ASA, has been found as a major factor contributing to infertility in men, accounting for approximately 10–30% of infertile cases (31). The autoimmune responses reduce fertility due to acrosome reaction (AR) impairment, defective capacitation, and DNA fragmentation of sperm. In addition, they lead to a decrease in sperm motility and concentration, damage to the acrosome reaction, morphological changes, and DNA fragmentation. The feasible pathogenesis of this damage is associated with oxidative stress. Some studies showed that ASA production is closely associated with TNF-α levels in infertile men, and that concentrations of TNF-α and ASA in SP have been observed to be

greater than in serum, indicating damage and local immune activation in the reproductive tract system (32). Scholars also found ASA in the SP of varicocele cases. Fertility evaluation after varicocelectomy showed that the effectiveness of varicocelectomy on reproductive function recovery is reduced by antisperm immune response. This study showed that high ASA values are associated with lower varicocele grade and worse prognosis (33). Seminal plasma immunosuppressive factor (SPIF) is one of the immunosuppressive substances in SP, with the ability to block and alter membrane antigens of sperm and inhibit immune system cells like NK cells, lymphocytes, complement systems, and macrophages (34). Furthermore, the presence of SPIF elevates the incidence rate, contagion, and transmission of several infections (e.g., AIDS). In cases of increased SPIF activity, the killing and recognition effects of immune factors on malignant tumors and pathogenic microorganisms are weakened, facilitating their spread. However, in cases of reduced SPIF activity during sexually transmitted diseases, the efficient inhibition of the lethal effects of immune factors on sperm cannot be applied, resulting in reduced implantation ability of fertilized ova as well as decreased sperm motility and viability. It has been shown that the body produces anti-SPIF antibodies in conditions such as trauma or infections of the reproductive tract; hence, the content of SPIF decreases and its activity is reduced. One study showed that SPIF antibodies can induce antibody-mediated agglutination of sperm, leading to reduced fertility. In this study, the levels of anti-SPIF IgA and IgG were determined in positive cases. Their results showed that the level of anti-SPIF IgG in the SP of infertile males was somewhat greater than that of IgA, though no significant differences were seen (35).

Seminal plasma factors and associated signaling pathways

The interaction between various SP components and their involvement in numerous signaling pathways contributes to the complex and multifaceted roles of SP in male fertility. This complexity makes it challenging to analyze each individual factor, its associated signaling mechanisms, and its specific impact on sperm function and interaction with the maternal reproductive system. Indeed, multiple overlapping signaling pathways are regulated by SP components, collectively influencing sperm maturation, motility, immune tolerance, and fertilization. The extracellular Zn^{2+} in SP attaches to the G protein-coupled receptor 39 (GPR39)-type Zn-receptor and then activates the AC-cAMP-PKA-Src-EGFR signaling cascade, which has been shown to be vital for hyperactivated motility (HAM) during the sperm capacitation process (Figure 2) (36). In addition, Fms-like tyrosine kinase-3 (FLT-3) has been introduced as one of the type III kinases that is increased in SP

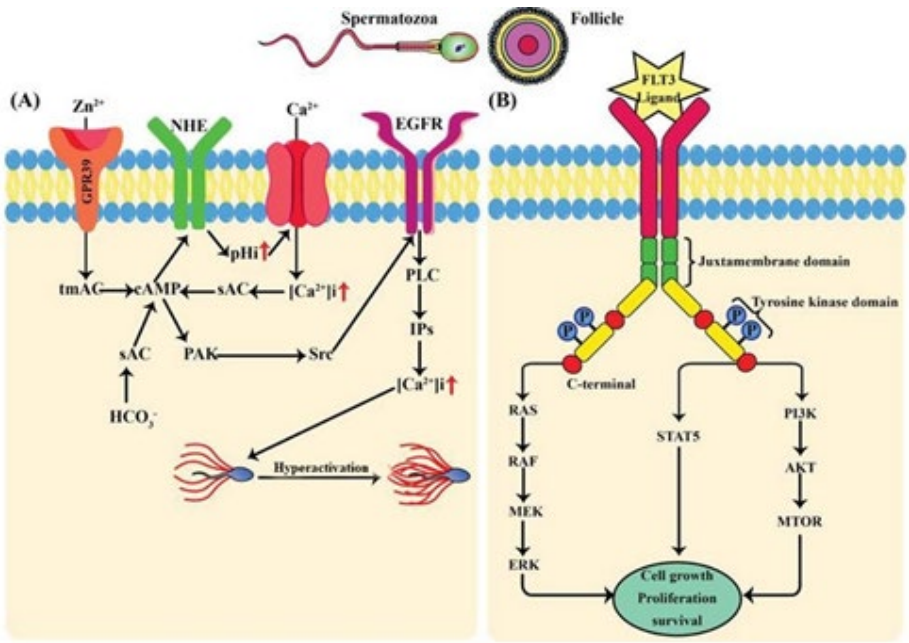

Figure 2. The functions of seminal plasma factors in capacitation. A: GPR39 is bound and activated by Zn^{2+}. Then, tmAC is activated by GPR39 for catalyzing the synthesis of cAMP. After that, cAMP will activate PKA, which in turn activates the epidermal Src growth factor receptor phospholipase C (SrcEGFRPLC) cascade, resulting in the formation of inositol triphosphate (IP3) that mobilizes Ca^{2+} from acrosome, resulting in additional enhancement of $[Ca^{2+}]$ and progression of the hyperactivated motility. B: FLT3 works as one of the cytokine receptors for the widespread FLT3 ligand (FL). Therefore, binding of FL to FLT3 leads to auto-phosphorylation of FLT3 & constitutive activation of its downstream effectors, such as MAPK/ERK, RAS/RAF/MEK, JAK/STAT5, & PI3K/AKT/mTOR pathways, each of them is a promoting cell cycle development, cells' proliferation (rapid growth), differentiation, & survival plays a crucial role

with high expression in infertile males. However, it was confirmed that inhibition of this kinase may suppress early embryonic development and fertilization via a PKA-dependent pathway, suggesting that FLT-3 is a crucial component in male fertility (Figure 2) (37). Certain signaling pathways may be affected by internal health and external environmental variables. For example, obesity has been observed to negatively regulate some proteins involved in the innate apoptosis pathway, activation of inflammatory responses, and antioxidant activity. One study showed that signaling pathways related to responses to oxidative stress as well as tissue homeostasis were influenced in patients with bilateral varicocele compared to healthy men (38). Some studies have shown that smoking affects signaling pathways related to inflammatory status, such as protein kinase A signaling, antigen processing and presentation, complement activation, regulation of cytokine-mediated signaling pathways, and regulation of the acute inflammatory response. These activities indicate an inflammatory response of SP to cigarette toxicity (39).

Bacterial infections and male infertility

Escherichia coli (E. coli)

It is widely accepted that gram-negative bacteria such as E. coli have the ability to colonize the genital tract in men. Also, these bacteria are correlated with accessory gland infection in men. E. coli bacteria can destroy germ cells and cause hypospermatogenesis. Lu et al. suggested that this bacterium can cause necrotic alterations in Sertoli cells and activate death pathways in the seminiferous tubules, which may be involved in impaired spermatogenesis (40).

Different strains of *E. coli* have a negative impact on sperm. Moreover, the severity of bacterial damage to sperm motility is related to the serotype and concentration of the bacteria. In this regard, scholars demonstrated the negative influence of the H strain of *E.*

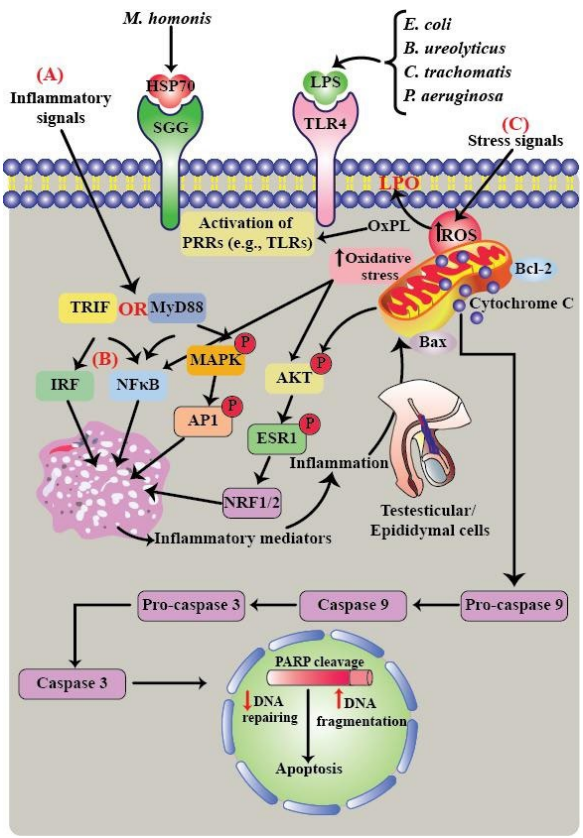

Figure 3. The pathophysiology of male infertility caused by bacterial infections is associated with inflammation and oxidative stress. Inflammatory stimuli such as LPS from gram-negative bacteria and HSP70 from *M.homonis* activate pattern recognition receptors (PRRs) in the epididymal and testicular cells., Activated PRRs initiate down-stream signaling through the primary response of myeloid differentiation (MYD88) & mitogen-activated protein (MAP) kinase pathways (IRF3). (B). Then, transcription factors like activated B cell nuclear factor-kappa light chain enhancer (NF-kB), interferon regulatory factor 3 (IRF3), activator protein 1 (AP-1) are activated by these cascades. (C) Excessive generation of ROS inhibits NF-kB transcription. In addition, ROS is capable of activating the transcription factors nuclear respiratory factor (NRF) 1 & 2 via the estrogen receptor (ESR) 1 & AKT (protein kinase B). The activated transcription factors, therefore, promote expressing the inflammatory mediators like tumor necrosis factor (TNF), interleukin (IL) 1, interferons (IFNs), tumor growth factor (TGF) B3, & nitric oxide (NO) that can result in the higher inflammations and finally work as OS stimuli, resulting in a feedback loop. Furthermore, OS may start apoptotic cascades via facilitating cytochrome-c (cyt-c) to get out of the mitochondria.

coli on sperm motility at different ratios (1:128, 1:16, and 1:2), whereas the strain NH-ATCC exhibited the same impact only at higher concentrations (41). However, one study showed that two strains of uropathogenic *E. coli* O6 (UPEC) cannot decrease sperm motility (42). One study showed that *E. coli* sperm agglutination factor (SAF) may reduce mouse sperm motility (43). *E. coli* inhibits sperm motility by attaching bacterial fimbriae to receptors on the flagellum or acrosome of sperm. Various receptors mediate the adhesion of bacteria to sperm. For example, pili and fimbriae are known bacterial adhesion structures. In addition, mannose receptors on human sperm have been introduced as mediators of adherence to *E. coli*. Also, results of a study using scanning electron microscopy (SEM) revealed the existence of a thin fibril between the acrosome, neck, and tail of damaged sperm and *E. coli* (44). Hemolytic *E. coli* strains produce cytolysin A, a subfamily of pore-forming toxins (PFTs). The toxin has been considered one of the calcium-dependent toxins that form pores by inserting into the cell membrane of the host. These pores release potassium and allow influx of mannitol, calcium, and sucrose, which subsequently leads to osmotic lysis and host cell death (Figure 4). It appears that one mechanism of action of this toxin is inactivation of the 3-kinase/protein kinase B (PI3K/AKT) signaling pathway (45). Another *E. coli* toxin, called Shiga-like toxin, can also affect sperm functions. It was found that this toxin is capable of inducing chromatin condensation, DNA fragmentation, cell membrane vesicles, cell size reduction, and formation of apoptotic bodies in Hep2 cells (Figure 4).

Bacteroides Ureolyticus (*B. Ureolyticus*)

Bacteroides ureolyticus is a species of gram-negative bacteria that can colonize the genital tract in men. It is associated with several specific sperm abnormalities, such as reduced total fructose content, greater numbers of short-tailed sperm, and greater numbers of epithelial cells (46). Several in vitro studies have shown that *B. ureolyticus* can affect sperm function and structure by reducing motility and damaging sperm membranes, particularly the lipid layers (47, 48). Gram-negative bacteria are known to release

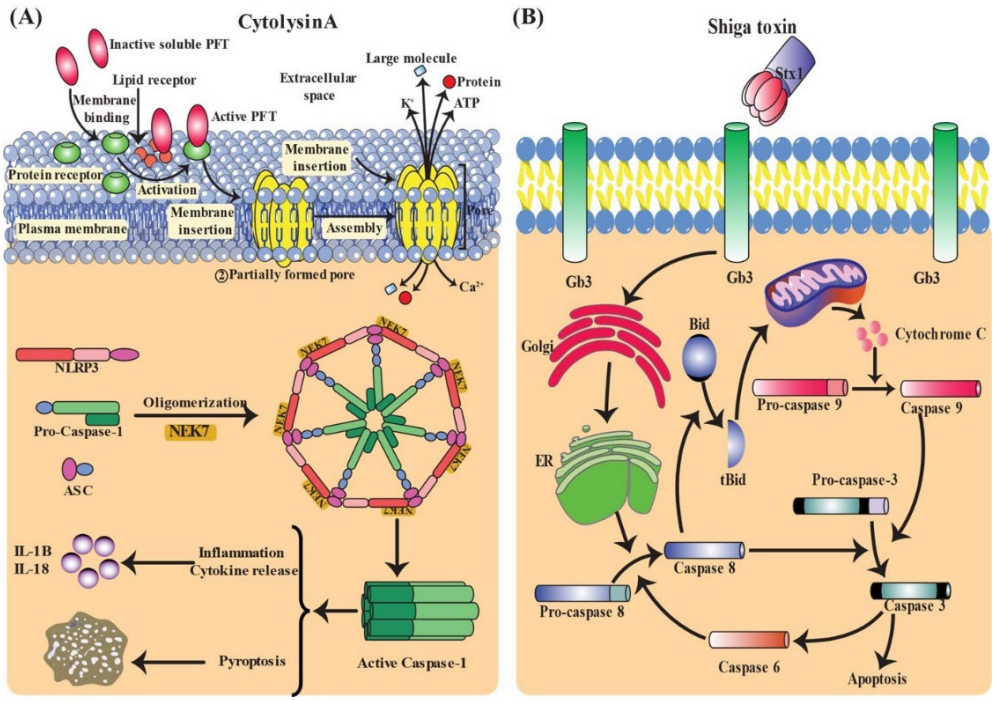

Figure 4. A: Mechanism function of *E. coli* toxins induced male infertility. A: Cytolysin A monomers that connect to target membranes. Upon membrane binding, insertion of cytolysin A into the membrane happens simultaneously with a sequential oligomerization mechanism that can result in the formation of a partially formed but active pore. This pore causes the leakage of minute cytoplasmic contents less than 2 kDa, such as Ca^{2+} and K^{+}, thereby changing ion gradients. This modification activated the NLRP3 gene. The development of a multimeric inflammasome complex is initiated by the oligomerization of NLRP3. The inflammasome complex allows for proteolytic cleavage and activation of caspase-1, allowing its release of inflammatory cytokines and pyroptosis. B: After internalization of toxin, activation of caspase 8 is observed immediately, triggering caspase-dependent & mitochondria-dependent apoptotic signaling pathways. Direct activation of caspase 3 is also possible by Caspase 8 that can then activate caspase 6 to form an amplification loop for activating the executioner caspase. In addition, BH3 domain containing protein (Bid) is cleaved by Caspase 8. Translocation of tBid molecules into mitochondria facilitates cytochrome c release. Finally, cytochrome C uses Apaf-1 & dATP to form apoptosome, which sequentially activates caspases 9 and 3. Retrograde transfer of holotoxin to the endoplasmic reticulum (ER) is necessary for apoptotic signaling.

lipopolysaccharide (LPS), which acts as an endotoxin. Lipopolysaccharide can upregulate cytokines, leading to induction of inflammatory responses. Studies have shown that inflammatory mediators may result in DNA fragmentation in ejaculated sperm and limit the fertilization ability of germ cells (Figure 3) (49, 50).

Chlamydia Trachomatis (*C. trachomatis*)

Chlamydia trachomatis as one of the gram-negative bacteria has been isolated from the male urogenital system. *Chlamydia trachomatis* has been known as one of the obligate intracellular bacteria and is responsible for sexually transmitted infections in both men and women. This bacterium has a distinctive developmental cycle in which it switches between two forms: an infective extracellular form called elementary bodies (EB), which is metabolically inactive, and an intracellular, proliferating form called reticulum bodies (ER), which is metabolically active. The genital tract periodically contains significant numbers of highly infectious EBs. In vitro study showed that localization of EBs can lead to increased tyrosine phosphorylation of human sperm causing apoptosis in it through the cysteine-aspartic acid protease (caspase) pathway (51). In this regard, there are some reports that *C. trachomatis* infection can decline the numbers of the normal sperms (52, 53). However, in other publications, no correlation was found between impaired spermatogenesis and *C. trachomatis* infection (54, 55).

A previous study reported a negative impact of EBs extracted from *C. trachomatis* serovar E on sperm motility (56). Furthermore, it was observed that incubation of normozoospermic human sperm with EBs may result in sperm apoptosis. First, EBs bind to the surface of sperm and invade them. After approximately 8 hours of latency, EBs convert into metabolically active reticulate bodies (RBs), which multiply through binary fission in the vacuole. When the replication cycle is complete, RBs are converted back into EBs and released into the extracellular space after sperm lysis (57). *C. trachomatis* can damage sperm by releasing mediators of the inflammatory response such as cytokines and reactive oxygen species (ROS). In addition, it has been reported that *C. trachomatis* infection can stimulate the generation of anti-sperm antibodies (ASA) in males and females (58). Moreover, a correlation has been observed between humoral immune responses to *Chlamydia trachomatis* infection and increased autoimmune response against sperm. During chlamydial genital infections, ASA can be produced, contributing to impaired fertility. These infections stimulate the release of proinflammatory cytokines from activated T cells, which in turn activate macrophages. As a result, macrophages are induced to phagocytose both *C. trachomatis* microorganisms and spermatozoa, further compromising sperm function and fertility (59).

Pseudomonas Aeruginosa (*P. aeruginosa*)

Pseudomonas aeruginosa has been introduced as one of the gram-negative opportunistic pathogens that contribute to human urinary tract infections. *P. aeruginosa* can disrupt the ability of germ cells to form in the seminal epithelium and thus impair spermatogenesis. Studies have shown that the presence of *Enterococcus faecalis* (*E. faecalis*) or *P. aeruginosa* in human semen can lead to a decrease in sperm count (60). In this regard, 3-oxododecanoyl-L-homoserine lactone produced by *P. aeruginosa* has been found to reduce sperm motility (61).

Mycoplasma Homonis (*M. homonis*)

Mycoplasma has been isolated from the urogenital tract in men and is a natural resident of the urethra, contaminating semen during ejaculation. They can cause infection through sexual contact and are therefore often referred to as sexual mycoplasma (62). *M. hominis* has been shown to interact closely with the membrane surface of the sperm plasma. Despite binding of *M. hominis* to the whole areas of the sperm, the interaction kinetics showed a pronounced affinity for the head and tail of spermatozoa (63). A sulfated glycolipid called sulfogalactoglycerolipid (SGG) is found on the external surface of the plasma membrane in mammalian male germ cells. It was reported that increased content of SGG in human spermatozoa provides a significant number of receptor molecules for *M. hominis*, through which it can attain adherence and successive internalization. Scholars reported a 70 kDa heat shock protein-related molecule as the SGG ligand in *M. hominis* (64). Hence, the disruptive interaction of *M. hominis* with various sperm cell structures may stem from the presence of spermatozoa at different stages of maturation and early capacitation during incubation. These physiological processes are characterized by dynamic changes in the distribution of surface proteins, increased plasma membrane fluidity, and alterations in enzyme activity. Such modifications render sperm more susceptible to microbial interference, potentially impairing their function and fertilization capability (65). Moreover, reports indicated *M. hominis* ability to invade spermatozoa, which may have implications for host persistence and immune responses (66). It seems that the basic virulence mechanism shown by *M. hominis* binding to sperm involves the release of reactive oxygen species (ROS), which result in lipid peroxidation, loss of membrane fluidity, damage to the host cell membrane, and finally lead to inability to hyperactivate the acrosome response. One complication of membrane disruption by ROS can be exposure of sperm antigens, which can lead to autoimmune reactions. *M. hominis* causes subtle damage to sperm, resulting in nuclear decondensation, denaturation or breaks of DNA single strands, and effects on sperm viability, motility, and morphology.

Conclusion

Various types of bacteria can colonize different regions of the male reproductive system such as the testes, epididymis, prostate, and urethra, leading to conditions like urethritis, orchitis, and impaired spermatogenesis. These infections can also cause structural and functional damage to sperm, including DNA fragmentation, vacuole formation, acrosomal disruption, membrane degradation, and mitochondrial dysfunction, ultimately resulting in poor semen quality and reduced fertility. Given the substantial negative impact of bacterial infections on semen parameters, it is essential to recognize the types of bacteria involved in genitourinary tract infections and understand their underlying mechanisms of action. This knowledge is crucial for developing effective strategies to diagnose and treat bacteria-induced male infertility.

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Author contributions

Hajar Hajian, Hamed Mirzaei, Zohreh Seyedi, Mitra Motallebi, Mohammad Esmaeil Shahaboddin contributed to manuscript drafting and data collection. All authors approved the final paper.

Conflict of Interest

The authors declared that they have no conflict of interest.

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