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INVITED REVIEW

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Implications of prostate inflammation on male fertility

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Abstract

The prostate is the seat of three major causes of morbidity: benign prostatic hyperplasia, prostate cancer and prostatitis, three conditions in which inflammation has been implicated. A state of inflammation of the prostate gland, originally incited by an infection, an autoimmune response, a neurogenic stimulus or another trigger may have consequences on prostate functionality. In fact, male fertility depends intrinsically on the content of prostatic fluid factors secreted by the prostatic epithelium. Taking into account that the prostate gland is the major male accessory gland that exerts essential functions for male fertility, a state of local inflammation can alter male fertility by either directly impairing sperm quality or, indirectly, by causing prostate dysfunction. In the present review, we summarise the current knowledge regarding prostatitis due to well-known infections such as *Escherichia coli*, *Chlamydia trachomatis* and other commonly identified microorganisms focusing on inflammatory markers detected during these infections and seminal quality and male fertility alterations reported. We also focused on type III prostatitis or chronic nonbacterial prostatitis/chronic pelvic pain syndrome, of unknown aetiology, in which inflammation of an autoimmune origin, neurogenic stimuli or another trigger have been proposed and fertility alterations reported.

KEYWORDS
fertility, infection, inflammation, prostate, spermatozoa

1 | INTRODUCTION

The prostate is the seat of three major causes of morbidity: benign prostatic hyperplasia (BPH), prostate cancer (PC) and prostatitis, three conditions in which inflammation has been implicated (Verze, Cai, & Lorenzetti, 2016). BPH is a condition extremely prevalent in male adulthood and senescence, affecting 42% of men in the fifth decade to almost 90% in men older than 80 years (Fibbi, Penna, Morelli, Adorini, & Maggi, 2010). PC is one of the most common cancers in men, and the risk is higher in men older than 55–65 years (De Marzo et al., 2007). In addition, prostatitis, which indicates a state of inflammation of the prostate, is the most common urologic diagnosis in men younger than 50 years and the third most common urologic diagnosis in men over 50 years (Khan et al., 2017). Currently, prostatitis is classified into four categories: acute (I) or chronic (II) bacterial prostatitis, chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) (III) that could be inflammatory (IIIa) or non-inflammatory (IIIb), and asymptomatic prostatitis (IV) (Khan et al., 2017). Type III prostatitis or CP/CPPS is the most common type of prostatitis encompassing more than 90% of cases. Patients typically experience dysuria, nocturia, contraction of the smooth muscle of the prostate and bladder neck, chronic pelvic and perineal pain, ejaculatory disturbances and sexual dysfunction (Khan et al., 2017).

As the prostate is the largest male accessory gland that exerts important physiological functions enhancing fertility, a state of inflammation can impair its normal physiology as well as directly

damage sperm cells after ejaculation thus altering male fertility potential. In fact, male fertility depends intrinsically on the content of prostatic fluid secreted by the prostatic epithelium (Alshahrani, McGill, & Agarwal, 2013; Verze et al., 2016). The key contribution of prostatic fluid to enhance male fertility is related to its role as a trigger for the molecular pathways involved in ejaculation, sperm activation and capacitation, and more importantly in evoking gene expression, cellular changes and tissue remodelling in the female reproductive tract and immune system, thus actively influencing fertility and fecundity (Robertson & Sharkey, 2016; Verze et al., 2016).

In the present review, we summarise the current knowledge regarding prostatitis due to infections by *Escherichia coli*, *Chlamydia trachomatis* (CT) and other microorganisms commonly identified in prostate fluids focusing on the inflammatory markers, seminal quality and male fertility alterations reported. We also focused on type III prostatitis, in which chronic inflammation of an autoimmune, neurogenic, endocrine or chemical basis have been proposed and sperm quality and male fertility alterations reported.

Overall, we suggest that a state of chronic inflammation of the prostate, originally incited by an infection, an autoimmune response, neurogenic stimuli or others may have consequences on prostate functionality. Prostate dysfunction together with the direct detrimental effects of the inflammatory milieu and/or infectious agents on sperm quality may compromise male fertility.

2 | PROSTATE PHYSIOLOGY

The prostate is the largest male accessory sex gland of the human reproductive tract. It is located at the base of the bladder and surrounds the proximal portion of the urethra, in which deliver the prostatic fluid during ejaculation (Aaron, Franco, & Hayward, 2016; Alshahrani et al., 2013). The prostate is composed of two major compartments, the epithelium and the stroma. Epithelial cells exert the gland secretory functions, while stromal cells provide the appropriate microenvironment and signals for gland homoeostasis besides constituting the supportive tissue (Aaron et al., 2016; Alshahrani et al., 2013). Prostate physiology is strictly dependent on androgens, whose secretion is regulated by the hypothalamic-pituitary–adrenal or gonadal axis. Interestingly, prostate epithelial cells express the enzyme 5α-reductase, which confers them the ability to convert serum testosterone into the more potent androgen di-hydrotestosterone. The latter, together with the expression of androgen receptor, are essential for the gland homoeostasis and function.

The main function of the prostate is to produce the prostate fluid that contains a complex mixture of factors that exert essential functions for reproduction and accompany and protect the sperm cells during their traversal through the female tract (Gilany, Minai-Tehrani, Savadi-Shiraz, Rezadoost, & Lakpour, 2015; Robertson & Sharkey, 2016; Zhao et al., 2016). Mature spermatozoa represent a minimal amount of the total ejaculate volume, while the main contribution to semen volume comes from the secretions of the seminal vesicles, the prostate and the epididymis (Verze et al., 2016; Zhao et al., 2016). Prostatic secretions contribute up to 30% of semen volume and contain several factors that control ejaculation, regulate the processes of semen clotting and liquefaction, sperm activation and capacitation, and also induce several changes in the cervix and endometrium and in the maternal immune system to ensure successful implantation and embryo growth (Kalinska, Meyer-Hoffert, Kantyka, & Potempa, 2016; Robertson & Sharkey, 2016; Zhao et al., 2016). Prostate secretions contain high amounts of zinc, citrate, calcium, phosphate, lipids, kallikreins (KLKs), antioxidant enzymes, polyamines, interleukins (IL), hormones, mRNAs and other factors important for sperm function and female tract tissue remodelling and immune regulation (Zhao et al., 2016). Prostate epithelial cells have the androgen-dependent ability to concentrate and secrete the highest amounts of zinc in the human body. Zn^{2+} plays several crucial actions in reproductive physiology. Prostate epithelial Zn^{2+} accumulation blocks the Krebs cycle ensuring the storage of high amount of citrate that would in turn be secreted to the seminal plasma. Moreover, Zn^{2+} acts as an active inhibitor of KLKs until ejaculation, when seminal vesicles-derived semenogelins activate KLKs (by sequestering Zn^{2+} by competition) allowing semen liquefaction (Jodar, Soler-Ventura, & Oliva, 2017). Sperm chromatin stabilisation is affected when Zn^{2+} levels are decreased and sperm DNA becomes vulnerable to factors that may lead to its fragmentation (Kalinska et al., 2016; Zhao et al., 2016). Moreover, Zn^{2+} is mandatory for the antibacterial activity of human seminal plasma that is essential for the immediate protection of spermatozoa against microbes at insemination in the vagina (Edström et al., 2008). Prostate epithelial cells have the rare ability to obtain energy by glycolysis rather than by the Krebs cycle. Their Zn^{2+}-dependent ability to block the Krebs cycle allows them to produce, store and then secrete high concentrations of citrate (Alshahrani et al., 2013; Verze et al., 2016). The prostate-derived citrate levels are 100-fold higher than those from the seminal vesicles. Citrate is essential for regulating semen pH and nourishing spermatozoa after ejaculation (Alshahrani et al., 2013). Prostate epithelial cells also secrete serine proteases KLKs, including KLK2, KLK3 (also known as the prostate specific antigen, PSA), KLK4, KLK5 and KLK14, into the seminal fluid at high concentrations. These serine proteases regulate semen clotting and liquefaction in concert with fibronectin and semenogelins in a Zn^{2+}-dependent manner (Alshahrani et al., 2013; Verze et al., 2016). Human PSA and KLK2 have largely been used as biomarkers of prostate pathology as their serum levels raise in many prostate diseases, including inflammation, BPH and PC. Finally, the prostate secretes many other factors, such as prostatic acid phosphatase, zinc-α2-glycoprotein, β- microseminoprotein, hyaluronidase, catalase, SOD, TGFβ, lipophilins, microRNAs, hormones and lipids, important for sperm physiology, male fertility and reproduction (Alshahrani et al., 2013; Gilany et al., 2015; Kalinska et al., 2016; Zhao et al., 2016).

Seminal plasma is not mandatory for successful reproduction in humans and most animals, as viable pregnancies can be initiated using epididymal or washed ejaculated spermatozoa in assisted

reproduction. However, cumulative evidence indicates that fertility and foetal development are compromised if spermatozoa and females are not exposed to seminal plasma (Robertson & Sharkey, 2016).

3 | PROSTATE INFLAMMATION: CAUSES AND CONSEQUENCES ON MALE FERTILITY

Prostate inflammation is triggered by acute or chronic infections of the gland. Besides, chronic inflammation is a hallmark in chronic nonbacterial prostatitis/CPPS (Barratt et al., 2010; Fibbi et al., 2010; Khan et al., 2017; Verze et al., 2016).

An important aspect to be taken into account for analysing the presence of inflammation markers and/or infection agents in prostatic diseases is to define the biological sample which would be the most appropriate. Prostate fluids can be analysed in samples such as expressed prostatic secretion (EPS), urine post-prostate massage and/or semen (Budía et al., 2006; Huang, Wang, Zhang, & Peng, 2018). First or middle voided urine is the specimen of choice for the detection of acute bacterial infections of the male genital tract. However, the reliability of some samples for an accurate diagnosis of infectious prostatitis was questioned as some studies indicate that semen or EPS are often positive for microorganisms in prostatitis patients with negative urine or urethral swabs cultures (Nickel et al., 2006). The two glass pre- and post-massage test is considered the "gold standard" method for localising infections of the prostate, as it has been proven to be reasonably accurate. Prostatic secretions are obtained by systematic massage of each of the prostate lobes. Bacterial prostatitis can be confirmed by the presence of greatly higher bacterial counts in urine post-prostatic massage when compared to the pre-massage urine sample (Nickel et al., 2006). Semen, which is routinely collected for analysis, might provide additional information of infections of the upper genital tract that may not be detected in first-middle voided urine or urethral swabs. However, it cannot be assumed that the inflammatory markers or microorganisms detected in semen certainly come from the prostate (Budía et al., 2006; Huang et al., 2018; Nickel et al., 2006). Nevertheless, some reports have recently revealed that semen presents higher sensitivity than EPS when analysing prostate infections. Thus, semen should be considered as a sample of choice for diagnosing bacterial prostatitis.

3.1 | Infectious prostatitis

Type I or acute bacterial prostatitis (ABP, 2%–5% of prostatitis cases) is an acute infection of the prostate caused by uropathogenic bacteria which may be a medical emergency. The most frequent causes of ABP are *E. coli* (responsible for more than 50% of cases), *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Pseudomonas aeruginosa*, and *Proteus* spp. (Khan et al., 2017). In sexually active individuals, *Neisseria gonorrhoeae* and *C. trachomatis* are also typical causes of ABP (Nagy & Kubej, 2012). Type I prostatitis presents with an acute onset of local (perineal and prostatic pain, polyuria, dysuria, incomplete bladder emptying) and systemic (fever, chills, and malaise) symptoms. As uropathogens are typically identified as causal aetiology, the disease responds well to antimicrobial therapy. Type II or chronic bacterial prostatitis (CBP, 2%–5% of cases) is a chronic or persistent infection of the prostate caused by *E. coli* (~80% of cases), *Klebsiella pneumonia*, *Proteus* spp., *C. trachomatis*, *Staphylococcus aureus*, the parasite *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *N. gonorrhoeae*, *Serratia marcescens*, *Enterobacter* spp., *P. aeruginosa* or others (Khan et al., 2017; Weidner et al., 2008). CBP manifests as only local intermittent symptoms (dysuria, urinary frequency and pelvic/perineal pain) that persist for 3 months or longer and is rarely a consequence of ABP (Weidner et al., 2008). Type II prostatitis also responds well to antimicrobial therapy. It is usually hard to detect bacteria in clinical samples when assessing CBP, possibly because bacteria may survive in the prostate for long periods (even in the presence of antimicrobial treatment) or to some difficult to culture microorganisms.

Other uropathogens causatives of prostatitis are fungi and viruses. Citomegalovirus, *Cryptococcus* spp. and *Candida* spp. have been proposed as possible causes of prostatitis in immunocompromised patients (Wise & Shteynshlyuger, 2006). The human papilloma virus (HPV) has also been isolated in patients with male accessory gland infection but the significance of its presence is still unknown (Cai, Wagenlehner, Mondaini, & D'elia, C., Meacci, F., Migno, S., Malossini, G., Mazzoli, S., & Bartoletti, R., 2014). Recently, it has been reported that ZIKA virus can be detected in semen and urine of infected men. Moreover, human prostate stromal and epithelial cells are an ideal niche for virus replication (Spencer et al., 2017).

Infertility affects approximately one in six couples worldwide and equally to both sexes. In fact, the incidence of male factor infertility is 7% and rising. Infection and inflammation constitute ~15% of all cases of male infertility. In that regard, the contribution of prostatitis to infertility is controversial (Schagdarsurengin, Western, Steger, & Meinhardt, 2016).

Uropathogens may alter sperm quality through different mechanisms: direct sperm damage, inflammation-induced damage or gland dysfunction. In this regard, caution should be taken when interpreting clinical and experimental data as the exposure of spermatozoa to microbes, leucocytes and inflammatory mediators may vary depending on the pathology. For instance, in epididymo-orchitis or orchitis spermatozoa are in close contact with inflammatory cells and mediators for days, which is different from leukocytospermia and increased levels of inflammatory mediators in semen consequence of infection/inflammation of the prostate, seminal vesicles or the lower urogenital tract. In the latter scenarios, sperm cells contact inflammatory cells and mediators after ejaculation and for shorter times. Thus, consequences of prostatitis or prostate-vesiculitis on semen/sperm quality and male fertility may be substantially different from epididymo-orchitis or orchitis.

Although scarce, available evidence indicates that type I prostatitis is not associated with either decreased semen quality or impaired male fertility. However, type II or CBP has been linked with decreased

prostatic excretory function, including reduced secretion of citrate, zinc, α-glucosidase and fructose (Khan et al., 2017). The mechanism of secretory dysfunction in prostatitis and the effects of lower concentrations of prostatic enzymes, trace elements and other factors in semen still remain unclear, but they could certainly impair male fertility (Condorelli, Russo, Calogero, Morgia, & La Vignera, 2017). In addition, leukocytospermia, increased seminal levels of TNF-α, IL-1β and reactive oxygen species (ROS), in association with reduced sperm quality, have been reported in CBP patients (Guo et al., 2010; Marconi, Pilatz, Wagenlehner, Diemer, & Weidner, 2009). Leukocytospermia, cytokines and ROS have largely been described to alter sperm quality.

3.1.1 | Escherichia coli

As mentioned above, *E. coli* accounts for 65%–80% of cases of type I and II prostatitis (Nagy & Kubej, 2012). Meta-analysis studies revealed that CBP patients present lower total sperm motility and progressively motile spermatozoa than control individuals (Shang, Liu, Cui, Han, & Yi, 2014). In addition, half of individuals with premature ejaculation were diagnosed with CBP, suggesting once more that chronic *E. coli* infection of the prostate may have a detrimental role on male infertility (Screponi et al., 2001).

Despite that clinical evidence, the mechanisms by which *E. coli* causes these deleterious effects on semen have not been clearly elucidated yet. However, in vitro studies provided compelling evidence indicating that *E. coli* can cause a direct toxic effect on spermatozoa. Also, sperm motility has been shown to be impaired by an adherent effect of *E. coli* resulting on the agglutination of semen and by modifications on mitochondria membrane potential (Barbonetti et al., 2013; Boguen, Treulen, Uribe, & Villegas, 2015). Moreover, haemolysin-producing *E. coli* strains cause more deleterious effects on spermatozoa than those strains unable to produce that virulence factor (Barbonetti et al., 2013; Verze et al., 2016).

On the other hand, it has also been shown that *E. coli* can cause sperm damage indirectly. The infection of the prostate with uropathogenic *E. coli* (UPEC) recruits and activates immune cells thus causing the release of ROS and cytokines, which impair sperm quality (Schulz, Sánchez, Soto, Risopatrón, & Villegas, 2010). Remarkably, a study on 100 infertile patients with prostatitis caused by *E. coli* infection indicated that only patients that eradicated the infection (after levofloxacin treatment) showed improvements in semen quality (Vicari et al., 2016). Although it is clear that *E. coli* infection has a detrimental role on male infertility, further studies are necessary to unveil the precise mechanisms.

3.1.2 | Chlamydia trachomatis

Chlamydia trachomatis (CT) is the most prevalent sexually transmitted bacterial infection worldwide. *C. trachomatis* infects the urethral epithelial cells and then can lead to an ascending infection to the prostate, seminal vesicles and the upper genital tract. Several reports have documented a prevalence of CT infection in patients with chronic prostatitis ranging from 8.3% to 27% (Mackern-Oberti et al., 2013). Chlamydial detection is performed by microbiological culture or molecular tests. Due to the fact that semen, urine after prostatic massage or EPS transit through the urethra, a diagnosis of prostatitis is a bit uncertain as potential urethral contamination may occur, thus limiting the test diagnostic value. Nevertheless, analysis of pure prostatic biopsies from chronic prostatitis patients certainly demonstrated the presence of CT in the absence of urethral infection (Toth et al., 2000).

Chronic male urogenital CT infections have been suggested as possible causes of male infertility in recent years (Mackern-Oberti et al., 2013). However, a clear association of male urogenital CT infections and altered semen quality and/or male infertility has not been proven yet (Redgrove & McLaughlin, 2014). In vitro studies showed that prostate epithelial cells respond to CT infection inducing several inflammatory cytokines and chemokines (Sellami et al., 2014). In addition, high levels of IL8 have been detected in semen from CBP patients (Mazzoli et al., 2007). Moreover, some authors reported an association of prostatitis caused by CT and decreased sperm concentration, viability, motility and normal morphology (Mackern-Oberti et al., 2013; Pajovic, Radojevic, Vukovic, & Stjepcevic, 2013). Conversely, most other studies provided compelling evidence indicating that CT urogenital infection neither alters semen quality nor impairs male fertility (Dehghan Marvast, Aflatoonian, Talebi, Ghasemzadeh, & Pacey, 2016; Mackern-Oberti et al., 2017). Interestingly, sperm alterations were reported in patients with co-infection of CT with *Mycoplasma* spp. or HPV rather than in patients with sole CT infection, suggesting that the sperm alterations observed were likely due to *Mycoplasma* spp. or HPV infections (Cai et al., 2014). These findings indicate that an exhaustive search for different uropathogens, besides CT, should be performed when screening patients. Moreover, evidence from animal models indicates that CBP caused by *Chlamydia muridarum* infection does not alter either semen quality or male fertility (Motrich, Sanchez, Maccioni, Mackern-Oberti, & Rivero, 2012).

Controversial results have also been reported in in vitro studies. Some authors have proposed that CT interacts with sperm cells, affecting their function and inducing apoptosis (Eley, Hosseinzadeh, Hakimi, Geary, & Pacey, 2005). On the contrary, it has been recently reported that in vitro sperm incubation with different serovars of CT or *C. muridarum* does not impair human or murine sperm quality respectively (Puerta Suárez et al., 2017).

In summary, currently available evidence does not support a clear relationship between prostatic CT infection and decreased semen quality and/or male fertility.

3.1.3 | Chronic nonbacterial prostatitis/Chronic pelvic pain syndrome

Type III prostatitis or CP/CPPS that is the most common genitourinary problem in adult males aged <50 years, representing 90%–95% of all cases of prostatitis (Breser, Salazar, Rivero, & Motrich, 2017), is poorly understood. This syndrome involves the presence of local signs and symptoms of inflammation for more than 3 months and does not respond to antimicrobial therapy. In this regard, no

underlying infections are identified when screening patients and its aetiology still remains uncertain. CP/CPPS comprises similar clinical phenotypes resultant from a combination of different putative pathophysiological mechanisms. Several hypotheses have been proposed including defective urothelial integrity and function, cryptic infections, autoimmunity, endocrine imbalances, pelvic floor muscle spasm or tenderness, voiding dysfunction, peripheral and central sensitisation and neuroplasticity, and others (Breser et al., 2017). Although cryptic or difficult to culture microorganisms may be involved, several studies have systematically failed to identify infectious agents as causatives of this pathology (Pontari, 2013). In recent years, cumulative evidence from studies in patients and animal models has indicated that this syndrome is a consequence of deregulated inflammation in the form of autoimmunity against the prostate (Breser et al., 2017). Data indicate that several factors may trigger chronic inflammation in the form of autoimmunity against prostate, fostering chronic prostate recruitment of Th1 cells, and different other leucocytes, including mast cells, which might be the main actors in the consequent development of chronic pelvic pain. While some authors have speculated that IL-17 would be involved in CP/CPPS, conclusive evidence of an actual involvement of IL-17 in CP/CPPS, or in mice models is currently lacking (Breser et al., 2017; Motrich et al., 2016). Consequently, the local inflammatory milieu and the secretion of inflammatory mediators secreted by recruited leucocytes may induce neural sensitisation leading to chronic pelvic pain development (Breser et al., 2017; Motrich et al., 2016). Pelvic floor dysfunction as increased pelvic floor muscle spasm or tenderness has been also proposed as responsible for CP/CPPS symptoms. In fact, spasms or tight knots or trigger points in the pelvic floor muscles lateral and anterior to the prostate have been shown in CP/CPPS patients. Moreover, neurogenic pain and inflammation has also been suggested to play a major role in CP/CPPS pathogenesis. It has been proposed that neurogenic processes, immune injury and mast cells may contribute to inflammation and trigger pain development in CP/CPPS (Nickel et al., 2007). Inflammatory stimuli are known to induce substance P, calcitonin gene-related peptide, and nerve growth factor (NGF) secretion from nerve terminals, resulting in plasma extravasation, oedema, and hyperalgesia, commonly referred to as neurogenic inflammation (Breser et al., 2017).

Cumulative data indicate that type III prostatitis or CP/CPPS patients have reduced semen quality. Different studies have reported sperm alterations in CP/CPPS when compared to healthy controls (Fu et al., 2014; Motrich et al., 2005). A systematic review and meta-analysis on 999 CP/CPPS patients and 455 controls from 12 independent studies have shown a clear negative effect on this syndrome on basic semen quality parameters (concentration, progressive motility and morphology, Fu et al., 2014). In fact, increased levels of inflammatory cytokines (IFN-γ, IL-1β, TNF-α, IL-6, IL-8), NGF and ROS, associated with reduced semen quality, were detected in seminal plasma from CP/CPPS patients (Lampiao & Plessis, 2008; Rivero, Motrich, Maccioni, & Riera, 2007). Animal models of CP/CPPS showed that prostate autoimmune inflammation is associated with increased levels of ROS, TNF-α, IL-1β, IFN-γ, reduced sperm concentration, motility and viability, and increased sperm apoptosis (Motrich et al., 2006). Interestingly, mating studies revealed that male fertility was significantly reduced in these animals (Bisht, Faiq, Tolahunase, & Dada, 2017). Inflammatory cytokines have been shown to significantly reduce sperm progressive motility and normal morphology, impair sperm mitochondrial function and induce sperm apoptosis (Bisht et al., 2017). Moreover, it is well-known that oxidative stress is highly toxic and detrimental to spermatozoa and causative of male infertility (Hu et al., 2016).

4 | FUTURE PERSPECTIVE

The study of the prostate physiology and its role on male fertility was neglected for decades. However, increasing enthusiasm and interest in the field have been experienced during last years. Male fertility not only requires spermatogenesis but also the coordinated functions of all the accessory glands of the male genital tract. The prostate substantially contributes to seminal plasma composition. Seminal plasma has a wide array of mediators that play a myriad of effects, such as preservation and capacitation of spermatozoa, and also modulation of the female tract and the immune system for ensuring proper implantation, embryo growth, pregnancy outcome and child health. Cumulative evidence indicates that infection and inflammation of the prostate are detrimental to sperm quality and male fertility directly or indirectly by causing prostate dysfunction. Ongoing and further research in the area will provide insights into the precise cellular and molecular mechanisms underlying these deleterious effects to benefit human reproductive health.

5 | CLINICAL IMPLICATIONS

Recent studies in the field have allowed a considerable advance in the current knowledge of prostate physiology and the consequences of infection/inflammation of the gland on male fertility. Different studies in patients and in vitro and in vivo systems have revealed that the prostate plays a major role in reproduction, and that its impairment might lead to male fertility alterations. In consequence, infections and/or chronic inflammation of the prostate should be carefully taken into account when assessing possible causes of male infertility in the clinical practice.

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