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Inflammatory mediators exert toxic effects of oxidative stress on human spermatozoa

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Abstract

Epidemiological studies regarding male infertility have revealed that more and more infertile men suffer from acute or chronic inflammation of the genitourinary tract, which often occurs without any symptoms. The inflammatory reactions within the male genital tract are inevitably connected with oxidative stress. Growing evidence indicates that imbalance between prooxidative and anti-oxidative substances in semen leads to metabolic and functional disorders of male germ cells and may be a primary cause of some types of infertility. The infectious factor and local tissue damage can lead to the infiltration of leukocytes to the inflammatory site. This is in an obvious way connected to the production and release of large amounts of reactive oxygen species (ROS), which trigger immune responses directed against the infectious agent, and the simultaneous secretion of numerous biological substances, thereby escalating the inflammation. Some of these factors are proteases and proinflammatory cytokines. Extended exposure of spermatozoa to ROS may lead to the peroxidation of sperm membrane lipids. Many studies point to the combined activities of inflammatory mediators in exerting toxic effects on spermatozoa. The local influences of biologically active substances released by activated leukocytes in the course of the inflammatory response and the mutual

interactions of various factors (bacteria, leukocytes, proinflammatory cytokines) at the site represent a complex puzzle.

Key words: Inflammatory factors, reactive oxygen species, peroxidative damage, semen

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The direct association between acute or chronic infection and/or inflammation in the male reproductive system and the subsequent development of infertility constitute important issues in contemporary medicine. The reduced semen quality during the inflammatory process can result from impairment of accessory gland function, obstruction of sperm transport, and dysregulation of spermatogenesis (Purvis and Christiansen, 1993; Comphaire et al, 1999). Most authors working on inflammation of the genitourinary tract suggest that the redox imbalance in semen acts as a very important mediator in the cause and effect relationship between semen infection and functional deficiency of germ cells (Wang et al, 1997; Ochsendorf, 1999; Vicari, 1999).

The processes that are crucial for fertilization, such as sperm hyperactivation, phosphorylation of tyrosine kinases during sperm capacitation, and the activation of cellular phospholipase A_2 in the acrosomal reaction, are strictly regulated by the redox system of spermatozoa (Goldman et al, 1992; de Lamirande and Gagnon, 1993; Leclerc et al, 1997). The same reactive oxygen species (ROS) that under physiological conditions are an inseparable element of the fertilization process, as well as being important regulatory factors in the control of spermatogenesis efficiency, may under pathological conditions (ROS excess) be responsible for structural, metabolic, and functional disorders of the male germ cells (de Lamirande and Gagnon, 1995; Griveau and Le Lannou, 1997; Aitken, 1999). This destructive effect of oxidative stress on male gametes is mainly associated with the peroxidative processes of sperm membrane components and DNA fragmentation (Twigg et al, 1998; Comhaire et al, 1999; Fraczek and Kurpisz, 2005; Aitken and Baker, 2006). However, the peroxidation of sperm membrane lipids is generally considered as the first marking point of germ cell damage induced by reactive oxygen intermediates, which in turn may lead to sperm dysfunction that results in the inability of sperm to penetrate the oocyte (Aitken and Fisher, 1994; Aitken, 1995; Sanocka and Kurpisz, 2004).

The ROS overproduction associated with inflammatory reactions may be primarily caused by pathological bacterial strains that colonize or infect the reproductive tract (Keck et al, 1998, Potts et al, 2000). The present review attempts to summarize the current state of knowledge on particular inflammatory mediators during male urogenital bacterial infections and their involvement in the origin and the degree of the oxidative stress that has serious consequences for sperm function.

Kinetics of the Inflammatory Process

In our previous studies, we proposed the kinetics of the infectious process in the urogenital tract based on the presence of bacteria and/or leukocytes in semen (Sanocka et al, 2003; Sanocka et al, 2004). In the course of the inflammatory process, the excessive production of ROS is most probably caused by additionally recruited leukocytes, which take part in this reaction and may disturb the balance of pro-oxidative and antioxidative factors (Wang et al, 1997; Ochsendorf, 1999). The inflammatory process involves mainly the accumulation and activation of leukocytes, mostly

phagocytes. Concomitant with the start of phagocytosis, the oxygen metabolism of leukocytes accelerates and is connected with the production and release of large amounts of superoxide anion (O^-_2) and hydrogen peroxide (H_2O_2) (Kovalski et al, 1992; Wang et al, 1997; Ochsendorf, 1999). At the same time, the activation of appropriate receptors and signal transduction pathways occurs, providing biologically active substances, such as proinflammatory cytokines. Secreted proinflammatory cytokines are the next mediators of the host response to infection, and they modulate the activities of the prooxidative and antioxidative systems to the advantage of the ROS burst (Rajasekaran et al, 1995; Sanocka et al, 2003). When the amounts of ROS exceed the potential of the antioxidant defense, peroxidative damage to the spermatozoa occurs (Fraczek and Kurpisz, 2005). It has been suggested that the reduced total antioxidant capacity (TAC) of seminal plasma is sufficient to ensure sperm quality (Sharma et al, 1999; Agarwal et al, 2003). Our experiments have also demonstrated that the remnants of oxidative stress in semen may be maintained over a long period of time after the infectious agent has been eradicated, and they further deteriorate the condition of the sperm. Oxidative imbalance is even more extensive in males who were infertile at the start of inflammation (Sanocka et al, 2004).

Bacteria

The bacteria responsible for semen infection may originate from the urinary tract or may be sexually transmitted (Purvis and Christiansen, 1993). The most frequently isolated microbial agents in semen are: *Streptococci* (eg, *Streptococcus viridans, S pyogenes*), coagulase-negative staphylococci (eg, *Staphylococcus haemolyticus, S epidermidis, S warneri*), and Gram-negative bacteria (eg, *Escherichia coli, Proteus mirabilis*). In addition, some anaerobic bacteria (*Bacteroides* sp, *Bifidobacterium* sp, *Propionibacterium* sp) and atypical mycoplasmas (*Ureaplasma urealyticum, Mycoplasma hominis*) have been detected (Eggert-Kruse et al, 1995; Merino et al, 1995; Willen et al, 1996; Jedrzejczak et al, 2005).

To date, there have been relatively few studies dedicated to the influence of particular groups and specific microbial species on sperm quality and/or their relationship with oxidative stress. The presence of infection in the male genitourinary tract has been correlated with a decrease in the number of sperm with good morphology (Menkveld and Kruger, 1998). Diemer and coworkers (Diemer et al, 2003b) have demonstrated the influence of *E coli* on sperm motility; incubation with leukocytes alone did not influence sperm motility, while coincubation of spermatozoa with leukocytes and *E coli*, significatly lowered their progressive movement in vitro. In another report, the same authors have reported that the pathogenicity of *E coli* is connected with its adhesive properties, which may lead to inactivation of and damage to the sperm acrosomal reaction. Electron microscopy analysis has revealed changes in sperm structure, mostly to the cell membranes of the head and midpiece but also to the internal and external acrosomal membranes (Diemer et al, 2000).

The connection between *B ureolyticus* and male infertility was first discussed over a decade ago. It was suggested that bacteria themselves or their toxins might affect sperm morphology (the prevalence of harmful changes to the tail was noted), increase the number of epithelial cells in the ejaculate, and diminish the levels of semen fructose, indicating specific colonization of seminal vesicles by these bacteria (Balmelli et al, 1994). Many studies have indicated that free radical species mediate the cytotoxic effects of these bacteria towards the male gametes as a consequence of peroxidative damage to the membrane structures.

Infections with *U urealyticum* are often considered as causes of male infertility (Shang et al, 1999; Potts et al, 2000; Han et al, 2003). The strong adhesive properties of these microbes, especially to the head of the postacrosomal region and midpiece, result in increased numbers of sperm with residual cytoplasm around the neck. The observed agglutination of sperm in the presence of mycoplasma may be related to diminished cell motility (Nunez-Calonge et al, 1998). The most toxic agents for spermatozoa are the metabolic products of *U urealyticum*, which include H_2O_2 and ammonia (NH_3). Although H_2O_2 is itself harmful to sperm, it is also a source of hydroxide anion (OH•), which is a highly toxic radical for cell membranes. Furthermore, *Ureaplasma* phospholipases A and C may influence changes in the lipid composition of the cell membranes of male gametes, leading to loss of integrity and increased permeability.

The prevalent view is that bacterial invasion is associated with leukocytospermia in semen (Fedder, 1996; Depuydt et al, 1998; Ochsendorf, 1999). Bacteria may also be implicated in asymptomatic leukocytospermia in infertile individuals (Esfandiari et al, 2002). On the other hand, the lack of leukocytospermia in semen does not preclude the onset of infection (Potts et al, 2000). The bacteria themselves or their products may contribute to ROS overproduction (Wang et al, 1997; Urata et al, 2001). Some researchers have observed higher levels of ROS in the semen of patients with positive microbial cultures (Mazzilli et al, 1994). The first detectable effects of the destructive influence of ROS overproduction in ejaculates during infection are visible as changes in the sperm membranes. In our latest report, we have shown a close association between the level of sperm membrane lipid peroxidation caused by bacterial infection and the decreased fertilization capacity of spermatozoa under in vitro conditions (Jedrzejczak et al, 2005). Although defects in the sperm membranes after earlier antibiotic treatment were not manifested in standard semen analysis, they clearly limited the fertilization potential of the spermatozoa. This indicates that even when an anti-inflammatory treatment eliminates the infectious agent and reduces the leukocyte concentration in seminal plasma it does not restore the semen redox balance, as revealed by a subsequent IVF procedure (Jedrzejczak et al, 2005).

In analyzing the influence of bacterial infection on the male reproductive tract, one should also take into consideration the induction of apoptosis. In somatic cells, the mechanism of apoptosis induced by bacteria depends on the type of pathogen and probably occurs through the activation of proapoptotic proteins, inactivation of antiapoptotic proteins or the improper adjustment of the receptor-ligand system located on the infected cell surface (Chen and Zychlinsky, 1994; Grassme et al, 2001). Villegas et al (Villegas et al, 2005) have recently demonstrated for the first time a significant increase in the percentage of annexin V-positive spermatozoa after their in vitro incubation with leukocytes and some bacteria. We cannot exclude the possibility that direct contact of bacteria or their toxins with spermatozoa is also an initial signal for germ cell death in the absence of leukocyte-generated ROS. Taking into account the notions that apoptosis is signaled by ROS and that the inflammatory process is strictly connected with the activation of oxidative metabolism, it would be interesting to analyze the influences of particular inflammatory mediators on apoptosis in specific sperm subpopulations with different fertilizing capacities.

To summarize this part of the review, we can state that microbial pathogens are the prominent agents of the infectious process and their participation in the creation of the oxidative stress phenomenon depends on the type of pathogen that colonizes or infects the male reproductive system. We still do not know if the microorganisms act destructively towards the sperm without mediation by the cells of the immune system, thereby directly inducing oxidative stress that leads to subfertility.

Leukocytes

The frequent presence of leukocytes in semen, including the major subpopulation of neutrophils, is inseparably connected with ROS production (Wolff and Anderson, 1988; Wolff, 1995). Since stimulated granulocytes show ROS-generating ability that is several hundred-fold greater than that of sperm, they can inflict damage on the male germ cells (Aitken and Fisher, 1994; Plante et al, 1994). The clinical significance of increased numbers of leukocytes in semen remains a subject of controversy. An increased number of semen leukocytes may result from disturbed spermatogenesis (Wolff et al, 1990; Thomas et al, 1997), the harmful influence of environmental factors, such as alcohol and tobacco smoking (Close, 1990), atypical sexual behavior or long-term sexual abstinence (Blackwell and Zaneveld, 1992; Anderson, 1995). However, the most frequent reason for the high proportion of phagocytic cells in ejaculates is genitourinary infection or inflammation.

The presence of leukocytes in semen is not pathological per se, since each ejaculate contains some leukocytes. The mean number of leukocytes in the semen of healthy men is about 17 x 10^4/mL of seminal plasma, which is composed of 50–60% granulocytes, 20–30% macrophages, and 2–5% T lymphocytes (Wolff and Anderson, 1988; Wolff, 1995). According to the World Health Organization (1999), a condition in which the number of leukocytes exceeds 1 x 10^6/mL of semen is defined as leukocytospermia, and this is considered to be the threshold value above which sperm dysfunction may occur. However, most authors agree that the determination of leukocyte counts in semen is important but not critical for the detection of infection or inflammation in the male reproductive tract (Rodin et al, 2003). Moreover, rather than the leukocyte numbers in semen, their activity levels decide the final effects of oxidative stress on spermatozoa (Kovalski et al, 1992; Sanocka et al, 2003). In addition, the presence of activated leukocytes in semen after elimination of an infectious agent may delay recovery of the normal oxidative balance in semen (Sanocka et al, 2003).

The origin of the leukocytes in semen, under physiological conditions, is difficult to explain. However, it has been assumed that under noninflammatory conditions, macrophages and lymphocytes infiltrate semen from the epididymis or rete testis, while granulocytes infiltrate mainly from the prostate and vas deferens (el-Demiry et al, 1985; Wolff, 1995). Under inflammatory conditions, WBC in the semen leak from the site of infection or inflammation. Taking into consideration the fact that the sperm is endangered by activated leukocytes (and their products) for quite a long period of time during their maturation, the greatest influences on spermatozoal function may be exerted during orchitis or epididymitis and during prostatitis. On the other hand, recent studies (Motrich et al, 2005; Motrich et al, 2006) have clearly demonstrated a close relationship between prostatitis and potential infertility even in nonbacterial prostatitis, as postulated previously (Leib et al, 1994).

There is also an ongoing controversy concerning the biological role of leukocytes in semen. Some reports have indicated the lack of any connection between the presence of leukocytes and semen quality or infertility status (el-Demiry et al, 1986; Tomlinson et al, 1992a; Tomlinson et al, 1993), and have suggested positive roles for these cells in the removal of dead or damaged spermatozoa (Tomlinson et al, 1992b). However, most authors point out the observed relationship between the increased number of leukocytes in semen and the deterioration of seminological parameters (Wolff et al, 1990; Yanushpolsky et al, 1996) or the fertilizing ability of sperm (Vogelpoel et al, 1991), which act mainly by influencing sperm motility and their potential for oocyte penetration (Maruyama et al, 1985; Kovalski et al, 1992). It seems likely that decreased sperm fertilizing ability is an early result of leukocytospermia associated with genitourinary

infection. Prolonged oxidative stress may contribute to the damage of the male reproductive organ involved in the inflammatory process. In the case of the male gonad, this damage is connected with disturbances in spermatogenesis and loss of sperm function. Along this line, the greatest danger can be inflicted by the chronic inflammatory process without clinical symptoms (Wolff et al, 1991).

The influence of WBCs on semen function depends on the dominating leukocyte subtypes and the intensity of inflammation. Individual susceptibility to infection and extent of tissue injury are also relevant factors (Wolff, 1995; Fedder, 1996). Irrespective of the different views on the source and the number of leukocytes in semen, most authors agree that leukocytes decrease the fertilizing potential of spermatozoa, mainly by inducing additional ROS release and the secretion of numerous active biological substances, such as proteases and proinflammatory cytokines, which then participate in and intensify the inflammatory process.

Proinflammatory Cytokines

The secretion of cytokines is one of the first signals from the innate host defense to combat infection. Cytokines are a large group of proteins generated by both the cells of the immune system as well as by the cells in surrounding tissues in response to external stimuli, inflicted injury or other cytokines. Cytokines participate in signal transmission between cells and perform regulatory roles in different biological processes, such as cell activation, proliferation, growth, differentiation, and mobility. They also show modulatory effects on inflammatory reactions. These include cytokines of the IL-1 family, such as interleukin (IL)-18, the IL-6 family, the superfamily of tumor necrosis factor (TNF) and interferons, IL-2, proinflammatory chemokines (eg, IL-8 and IL-12), and IL-15 (Feldmann and Saklatvala, 2001). The course of the inflammatory reaction depends on the levels of cytokines produced, as well as the presence of cytokine inhibitors and their specific receptors and/or antagonists. A characteristic feature of proinflammatory cytokines is that they are pleiotropic, so they may act in different directions. When they occur together, they can act synergistically, additively or antagonistically on the function of the target cell. Proinflammatory cytokines facilitate the development of inflammatory reactions by acting in concert to cause: 1) cell proliferation (IL-1, IL-2, IL-12, and IL-18); 2) chemoattraction of leukocytes to the site of inflammation (IL-1 and IL-8; 3) activation and differentiation of leukocytes (IL-1, IL-2, and IL-6), and 4) induction of apoptosis (IL-1ß, IL-18, and TNF-α) (Feldmann and Saklatvala, 2001) (Table).

Proinflammatory cytokines usually act locally, since they are produced by locally activated cells or produced temporarily after the stimulus has been activated. In the male gonad, cytokines are also produced physiologically and are involved in the normal function of the organ (Hales et al, 1999; Soder et al, 2000; Diemer et al, 2003a). In this respect, they appear as the natural components of seminal plasma (Maegawa et al, 2002). Moreover, some cytokines act as regulators of the physiological levels of ROS in seminal plasma (Buch et al, 1994; Depuydt et al, 1996). The main source of cytokines in the male gonad is testicular macrophages, although some cytokines (IL-1 and IL-6) are also produced by the cells of rete testis, which include the Leydig and Sertoli cells (Cudicini et al, 1997). The participation of some cytokines in the regulation of fertility is dependent upon their concentration. For instance, the IL-12 level correlates with the density and morphology of sperm cells, which suggests a certain biological role for IL-12 in male infertility (Naz and Evans, 1998). In turn, using human recombinant IL-6, capacitation and acrosomal reaction of sperm can be induced and the proportion of penetrated oocytes is increased (xenogeneic test of human sperm-hamster oocyte penetration) (Naz and Kaplan, 1994b). On the other hand, increased IL-6 levels

have been observed in the seminal plasma of infertile males (Naz and Kaplan, 1994a). High levels of certain cytokines in semen are often linked with a decrease in the quality of the seminological parameters (Gruschwitz et al, 1996). The same cytokines that act as elements of immunomodulation for the male gonad appear in large concentrations in semen during infection and when the tissues are damaged. Their participation in inflammation is closely connected with the accompanying leukocytospermia (Shimoya et al, 1993; Depuydt et al, 1996; Comphaire et al, 1999).

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Connections between activities of proinflammatory cytokines and semen parameters

Some authors have suggested that particular cytokines modulate the expression of genes responsible for the redox system in semen (Shimoya et al, 1993; Naz and Kaplan, 1994a). For instance, an increase in ROS production by human sperm was observed after the addition of IL-1α, IL-1ß or TNF-α, the result of which was an increase in sperm membrane lipid peroxidation, as measured by the MDA level (Buch et al, 1994). However, many studies have demonstrated the cooperativity of proinflammatory cytokines with other inflammatory mediators to generate toxic effects at the reaction site (Das, 1991; Rajasekaran et al, 1995). Zalata and coworkers (Zalata et al, 1995) have documented an increase in lipid peroxidation after an in vitro incubation of sperm with PMA-stimulated leukocytes, which suggests a decrease in the biological value of sperm cell membranes in the environment of oxidative stress. This type of observation argues in favor of the hypothesis that interleukins do not act separately but in connection with other mediators of the inflammatory process (Wolff, 1995). It seems likely that leukocytes mediate the induction of ROS generation by proinflammatory cytokines. In addition, it cannot be excluded that the oxidative stress that appears in leukocytospermia is exerted by the increased levels of the cytokines themselves (Rajasekaran et al, 1995). In this situation, ROS (generated by leukocytes) acts synergistically with proinflammatory cytokines to exacerbate the destructive environment for the spermatozoa.

IL-1ß is a well-known proinflammatory cytokine that is especially important for testicular physiology. It is involved in autocrine and paracrine regulation of local control of spermatogenesis and spermiogenesis, and constitutes one of the elements of immune privilege in the testis (Huleihel et al, 2000; Soder et al, 2000; Fiszer et al, 2003; Rozwadowska et al, 2005). This cytokine is responsible for the development and maintenance of the immune and inflammatory responses to invading pathogens. An increase in IL-1ß expression in the testis during local infection or inflammation is associated with decreased testosterone production by Leydig cells and decreased intensity of spermatogenesis, probably mediated through apoptosis (Huleihel and Lunenfeld, 2004). The effect of IL-1ß on semen quality is hotly debated in the literature.

Camejo and coworkers (Camejo et al, 2001) have suggested a relationship between the IL-6 level in semen plasma and the intensity of sperm membrane peroxidation. IL-6 is principally produced by monocytes/macrophages and its most important functions include the stimulation of B-lymphocyte differentiation, the activation of T lymphocytes, and the stimulation of acute phase protein release. High levels of IL-6 and/or MDA in the seminal plasma of infertile males have been reported (Camejo et al, 2001; Furuya et al, 2003). The chemotactic properties of IL-8 cause an influx of leukocytes into the site of inflammation and enhanced production of ROS, which most likely are connected with its harmful influence on sperm cell membranes. The high levels of IL-6 or IL-8

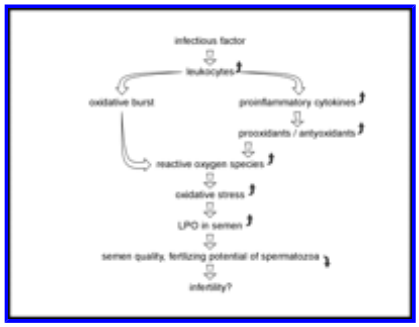
present during persistent inflammation augment the peroxidation process and affect sperm function, with subsequent development of infertility. We support the view put forward by several authors that the elevated levels of IL-6 or IL-8 in seminal plasma can be sensitive markers of the early phase of the inflammatory process in the male genitourinary tract, which can be used to initiate appropriate anti-inflammatory treatment (Depuydt et al, 1996; Eggert-Krusse et al, 2001; Sanocka et al, 2003).

Another proinflammatory cytokine that may be harmful towards sperm is TNF-α. Buch and coworkers (Buch et al, 1994) have reported increased MDA levels in semen after incubation with recombinant TNF-α. TNF-α, which is one of the major cytokines produced during inflammation, is secreted predominantly by monocytes and macrophages, mainly after contact with lipopolysaccharide (LPS). The cytotoxic influence of TNF-α is augmented by ROS and phospholipase A_2. It is possible that the toxicity of TNF-α for the sperm membranes is increased when other cytokines are present (unpublished data).

IL-12 has been detected in seminal plasma samples from both fertile and infertile males. The higher IL-12 levels observed in the seminal plasma samples of fertile males compared to infertile ones suggests the participation of this cytokine in the physiological functioning of the reproductive system (Naz and Evans, 1998). However, harmful effects of IL-12, such as through the induction of IL-18, on sperm cannot be excluded.

IL-18 belongs to the large IL-1 superfamily, and although it is structurally similar to IL-1 family members, it differs in terms of mode of action. It is not only produced by the cells of the immune system, such as monocytes and macrophages, in response to the LPS, but can also be released from keratinocytes, most epithelial cells, and osteoblasts (Dinarello, 1999). The proinflammatory activity of IL-18 is mostly linked to the stimulation of proliferation and the cytotoxicity of natural killer (NK) cells and T lymphocytes, among others, through the induction of IFN-γ production. IL-18 is augmented by IL-12 (Munder et al, 1998). In turn, IFN-γ, which is induced by both IL-18 and IL-12, stimulates macrophages to produce TNF-α, NO•, and ROS as part of the defense against infectious agents (Dinarello, 1999; Nakanishi et al, 2001).

A pathological role for IL-18 has been postulated (Fassbender et al, 1999; Tsutsui et al, 2000; Matsui et al, 2003; Maerten et al, 2004). The overproduction of this proinflammatory cytokine, particularly in combination with IL-12, may be dangerous both to the cells of the immune system as well as to other cells and tissues of the body. IL-18 plays a role in the pathogenesis of many other types of disease (eg, autoimmune disorders of the liver, skin, and kidneys, and degenerative rheumatoid inflammation) through the induction cell apoptosis. A recent report has described the participation of IL-18 in harmful effects on semen quality in infertile men with urogenital infections. Moreover, some authors have suggested that IL-18 in seminal plasma serves as another diagnostic marker for male genital tract infections (Matalliotakis et al, 2006). Assuming that oxidative stress leads not only to an uncontrolled increase in the concentration of reactive oxygen metabolites, but also to the failure of both the enzymatic and nonenzymatic members of the antioxidative system, we cannot exclude that IL-18 acts also through changes in the activities of enzymes that protect the sperm against these damaging metabolites. A clear relationship between increased IL-18 and decreased glutathione peroxidase (GPx) and selenium levels in the blood serum has been noted, for example in patients with acute pancreatitis (Wereszczynska-Siemiatkowska et al, 2004). The assessment of membrane peroxidation and/or apoptosis in spermatozoa could be helpful in explaining the pathological role of IL-18 during male reproductive tract infection or inflammation.



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The proposed kinetics of the infectious process showing the relationships between infectious factors, leukocytes, and proinflammatory cytokines.

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It should be emphasized that infection or inflammation of the male reproductive tract can be a cause of the increased oxidative stress. The inflammatory mediators individually enter the local process and intensify the redox imbalance, initially in the reproductive tract and later in the semen, which determines the magnitude of the interaction between toxic oxygen metabolites and cell macromolecules, and which in consequence affects the fertilizing potential of germ cells (Figure). The course of the inflammatory process and its effect on sperm depends on the type of initiating factor, the durations of activity of inflammatory mediators, and the initial condition of the antioxidant system in the semen. Prolonged infection or inflammation that occurs without any distinct clinical symptoms usually converts into a chronic subclinical process that can ultimately lead to persistent sperm damage and subsequent infertility. Since infections are often found in the semen of males whose infertility has not yet been assessed, rapid initiation of anti-inflammatory treatment is indicated before the reproductive potential of the sperm is restricted. Future research should concentrate on the proper diagnostic and treatment algorithms for male infertility that is caused or complicated by bacterial infections of the male genitourinary tract. Parallel studies under in vivo and in vitro conditions should provide a better understanding of the harmful effects of particular inflammatory factors, such as pathogenic microorganisms, leukocytes, and proinflammatory cytokines, and their influences on sperm oxidative metabolism.

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