Reproductive Inflammatory Mediators and Male Infertility

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Disruption of semen quality in cases of testicular and accessory gland infections, owe to altered spermatogenesis, sperm maturation and/or transport. The impact depends on the intensity, duration of progression, mediators of the inflammatory process and individual susceptibility to the infection. Interactions among the mediators with immunological cells and other regulators affect sperm function and have been reported to be associated with male infertility. However, the issue is still under debate and paves several dimensions of research in this realm. The summarized discussion of articles about the current knowledge on male reproductive tract inflammation and causative agents with its consequences on male reproductive functions have been included.

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Infertility refers to incapability to conceive even when a couple performs regular unprotected sex for a period of consecutive two years. The worldwide prevalence of infertility is predicted to be around 15% of all sexually active couples.1,2 Male factors contribute to at least half of the overall infertility cases, either solely or in association with female factors. Male infertility is multivariate with a wide range of causatives, most of which are yet to be disclosed. Male reproductive system can be compromised by various infectious agents. Genitourinary infections reportedly account for approximately 15% of male infertility cases, affecting testis, epididymis, and male accessory glands.3

Male reproductive system is anatomically and functionally immunoprivileged with special immune microenvironment designed to protect the testicular cells including the vulnerable germ cells.4 An array of microorganisms is identified with potential to infect male reproductive tissues via hematogenous dissemination or direct invasion into the male reproductive tissues and cause severe impairments to reproductive functions. In the event of testicular microbial infections, testis is armed with a special innate immune system.4 Testicular cells, prominently the Leydig cells, Sertoli cells and germ cells, have been shown to possess innate immune system and their regulatory counteracting mechanism. The precise operating mechanisms of this immune defence system remain uncertain, though. One of the commonest ways of activation of innate immune responses in testicular cells is by triggering the Toll-like receptors (TLRs) pathways. The TLRs induce release of inflammatory mediators, cytokines which include interleukins (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, and interferon (IFN) -α and -β. Studies demonstrated that activation of testicular TLRs, especially, TLR3 and TLR4 lead to disruption of steroidogenesis. Inflammation-induced testicular impairment is evident, the information about the role of TLRs along with the associated mechanism in male reproductive inflammation need a detailed evaluation which might be a point in direction of understanding the ways to mitigate the male infertility due to inflammatory factors.5

Testicular infections involve leukocytes migration and infiltration causing an elevated levels of seminal plasma leukocyte numbers. Leukocytes are common constituents of seminal plasma even in healthy and fertile male infections. These leukocytes are the main sources of reactive oxygen species (ROS). During an inflammatory process the number of seminal leukocytes increases and are activated leading to a condition referred to as leukocytospermia. In such condition, leukocyte mediated ROS production and induction of oxidative stress (OS) can significantly deteriorate sperm morphology and functions through lipid peroxidation, damage to the intracellular components, and sperm DNA fragmentation. These may account for reduced semen quality and lead to male infertility, although further detailed interventions are needed to draw conclusive remark on the association of seminal leukocytes with male infertility.6 Such leukocytes also secrete cytokines, a group of small proteins that are essential for cell signaling. Cytokines can be pro-inflammatory and anti-inflammatory. They also aid...
the interaction between the leukocytes and other immune-reactive cells, such as macrophages. Several aspects regarding the association of inflammation, pro-inflammatory mediators and male infertility need interlinked analysis where the roles of cytokines and adipokines in the context of understanding the mechanisms of inflammation-induced alterations in semen quality preludes.7

Systemic infections induced by various factors such as obesity have been found to be major contributors in male infertility.8 The obesogenic endogenous changes drive immune responses towards chronic inflammatory process via activation of T helper cells (TH)-1. Such a systemic inflammatory condition adversely affects all the major organs including the testes, epididymis, and male accessory glands. The pro-inflammatory mediators including the cytokines interfere with the intricate reproductive regulations by the hypothalamic-pituitary-gonadal/testes (HPG/HPT) axis and thereby affect testicular functions. In fact, impaired steroidogenesis and spermatogenesis lead to hypogonadotropic hypogonadism and deteriorated semen parameters. In addition, obesity-induced systemic inflammatory responses may stimulate the overproduction of ROS establishing testicular OS, which in turn may disrupt endocrine regulations of male reproductive functions or can also directly damage sperm membrane, sperm chromatin integrity and epigenome. Thus, the explanations about the association of obesity and male infertility through the induction of systemic inflammatory processes have been discussed,9 which will aid further therapeutic interventions in management of infertility in obese male. The associated factor, the age along with (or) age associated inflammation have played a role in understanding the reducing fertility or sperm quality in men.9

The field of understanding about (epi-)genetic correlation with male infertility have potential application towards ratification of problem using molecular level gentic tools.10 The environmental and life style factors associated (epi-)genetic changes are known to degrade the sperm quality. Abnormal epigenetic changes have been proposed as an important causative factor for infertility in men. Abnormal DNA methylation, histone modification, altered non-coding RNAs have been well documented as in pathological conditions such as oligospermia, azoospermia, asthenospermia and tetratospermia in males; the factors lead to induction of infertility in men.10

Non-hormonal medicinal treatment, which involves the use of anti-inflammatory, antioxidants, fiber compounds, vitamin supplementation and oligo-elements, can be given to men with idiopathic or non-curable oligoasthenoteratozoospermia and with unexplained infertility, given that most cases are induced by inflammation and/or oxidative stress. The therapies include different antibiotics for exact pathogenic strains, anti-inflammatory medication targeted at particular infections, and the use of antioxidants separately or in combinations to reduce the OS.11 With lack of consensus on the dosage, duration and effects of non-hormonal treatment on male infertility, this special issue provides knowledge of how antioxidants, anti-inflammatory drugs and antibiotics treatment in reproductive tract infections are associated with amelioration of male fertility parameters. The nanomedicine formulations containing conjugates of nanoparticles12,13 and other nanosystems incorporating the drugs for inflammation, baterial infections treatment, genital tract infection drugs, biomarkers of human fertility, nanoparticles alone used as antioxidants impact the spermatogenesis cells, sperm quality, sperm functions and infertility.14

In line of understanding the factors and molecular intricacies of male infertility, the current knowledge advances have been presented through compilation of selected articles3–11 that comprehends all the major aspects of infection and inflammation mediated male infertility or subfertility.

- Editors

REFERENCES