

Review of Effects Different Infections on Male Fertility

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ABSTRACT

Infection is process of multi-factorial that is induced via a parasite, virus, or bacterium. It might bring about several diseases; include cancer, infertility and obesity. At the current study, we concentrate the attention on male fertility and infection association as alteration. Different studies were proposed that effecting infection is correlated with infertility. Thus, we review some effect on infertility risk and infection.

1. INTRODUCTION:

Male infertility is because of low production of sperms, abnormal function of sperm or blockages which blocks sperm delivery. Injuries, illnesses, problems of chronic health, choices of lifestyle and other factors might play a function in infertility of male [1]. The infection source is complex, infection source was divided into 3 groups: hepatitis B virus, virus i.e. mumps virus, virus of human papilloma, virus of herpes simplex, and virus as human immune-deficiency; bacteria, i.e. *Chlamydia trachomatis* and *Helicobacter pylori*; and parasite, i.e. *Toxoplasma gondii*. 1st, we review infertility and such infections association. Due to genetic effect might play crucial duties in regulation fertility infection. Also, genetic influences were discussed on infertility, basically the gene polymorphisms effecting infertility and infection in the coming parts. Male urogenital tract infections potentially are curable male infertility causes [2]. WHO considers prostatitis, urethritis, epididymitis and orchitis as male infections of accessory gland (MAGIs) [3].

Medical causes

Male fertility problems reasoned to a number of medical treatments and health issues which include the followings:

- **Varicocele;** is veins swelling that drains testicle. It's mostly revealed reversible male infertility cause. Despite the unknown real reason in which infertility caused by, it might in relation to abnormal temperature testicular regulation. Varicoceles result in sperm quality reduction [4].
- **Infection.** Few infections may interfere with production of sperms or its health or may promote scarring which blocks sperm passage. Such is including testicles or epididymis inflammation as well as some transmitted sexually infections, include HIV or gonorrhea. Despite few infections may lead to testicular permanent damage, mostly sperms may remain retrieved[5].
- **Issues of ejaculation.** Ejaculation as retrograde takes place if semen is entering bladder while orgasm where it should emerge out of penis tip. Different health cases cause

ejaculation being retrograde, include injuries of spinal, diabetes, medications, and bladder surgery, urethra or prostate [6].

- **Sperm attack by antibodies.** Antibodies of anti-sperm are immune cells system that identify mistakenly sperm as invaders being harmful and try to eliminating them [7].
- **Tumors.** Nonmalignant and cancers tumors may influence directly organs of male reproductive, via hormones released from glands which associated with reproduction, i.e., gland of pituitary, or via unknown reasons. In few situations, radiation, surgery, or chemotherapy for tumors treatment may influence fertility of male [8].
- **Imbalances of hormone.** Infertility may be resulting from testicles abnormality or disorders in which influencing other systems of hormones include pituitary, hypothalamus, adrenal, and thyroid glands. Hypogonadism of male due to testosterone being low and other problems related hormones have underlying possible causes [9].
- **Tubules defects which transport sperms.** Various tubes transport sperms which might be blocked for different reasons, include surgery causing inadvertent injury, infections being exist, trauma or development being abnormal, i.e., with fibrosis as cystic or similar conditions inherited [10].
- **Defects on chromosome.** Disorders inherited i.e., Klinefelter's syndrome — where a born male with 2 chromosomes of X and one chromosome of Y (instead of one Y and one X) — causing male reproductive organs abnormal development. Other genetic syndromes associated with infertility include cystic fibrosis, Kallmann's syndrome and Kartagener's syndrome [11].

Causes by Environment

High exposure to specific environmental factors i.e., toxins, heat, and chemicals may minimize production or function of sperms. Certain reasons including:

- **Chemicals being Industrial.** More exposure to toluene, benzenes, pesticides, xylene, herbicides, lead, painting materials and organic solvents may lead to low counts of sperms [12].
- **X-rays or Radiation.** Radiation exposure leads to sperm reduce production; despite it eventually will mostly is returning to normal. With high radiation doses, production of sperm can permanently be minimized [13].
- **Testicles overheating.** Temperatures increasing impair function and production of sperms. Despite inconclusive, limited studies, frequent saunas use or tubs being hot might impair temporarily count of sperms [14].

2. ALTERATION OF FERTILITY AND INFECTION:

2.1 Fertility and infection virus mumps:-

Mumps defined as droplet contact disease which transmitted to human through tract of respiratory. Viruses are multiplying at upper mucosa respiratory tract and transported to organs of affinity, i.e., pancreas, the internal ear, and mammary glands, ovaries, and testis. [15]

Virus of Mumps is virus of RNA that leads to reactions of inflammation. Mumps infections virus leads to clinical variable symptoms. At infection beginning, testes were attacked by virus in which testicular parenchymas were destroyed and androgen production is reduced. [16] Often, they cause parotitis and fever where about male adolescents of 30% of mumps are developing orchitis. [17] Due to orchitis of common complication in males, sometimes the disease is developing in patients of adults.

Studies previously conducted, it consist 300 mumps orchitis patients were performed (1951-1970). After mumps orchitis, deterioration being cytogenic,

regarding morphology of sperms, is an effect of long-lasting. Spermiogenesis, greatly was disrupted in patients as half. Various patients of not atrophied testes, fertility being poor were detected as persistently. Based on such observations, morphology of sperms was mostly affected of studied features, and count of sperms may be the least influenced. [18] It may be concluded that virus mumps infection is factor of risk for infertility of male.

2.2 Infertility and infection related to B virus of hepatitis

B virus of hepatitis (HBV) infection was detected as related to declined sperm chromosome function and instability [19] and impairing sperm morphology and viability. [20] Recently, it has been confirmed that sperm possibly is a vector for HBV vertical transmission. [21] Nevertheless, not much is known regarding HBV infection effects on functions of sperms that are crucial for fertility of such carriers of HBV.

HBs is the HBV basic component that is enveloping proteins, thus, its influences on functions of sperms, i.e., fertilizing sperm ability, motility, and the following pathways need more studies. [19] Another studies mention that infection of HBV is inducing various effects on chromosomes of sperms. In situ, technique of fluorescence hybridization able to visualize HBV sequences of DNA which is integrating into chromosomes of sperms. Eventually, HBV is entering germ male line and integrating into genome. [22].

2.3 Infertility and infection of *Chlamydia trachomatis*:

Chlamydia trachomatis is bacterium of intracellular requires cells being live for multiplication. Several reports have showed the association between quality of semen and infection by chlamydial. Some studies as *in vivo* and *in vitro* attempted to report the association between markers and infection by chlamydial in spermatozoa. Causal establishment relationship between infertility of male and chlamydia is of significant influences on health of public [23].

2.4 Infertility and infection of *Toxoplasma gondii*:

Toxoplasma gondii is a common parasite of protozoan infecting animals of warm-blooded, include both humans and mice. Almost, $\frac{1}{3}$ of population (human) has been subjected. [24] About 50% of population is infecting and developing toxoplasmosis as disease that is commonly zoonoses parasite worldwide. At various places within any locality and among several groups of population according to different cultural lifestyle, social, and environmental elements, always *T. gondii* prevalence varies. [25].

In human population, there are correlations between *Toxoplasma* infection and quality of sperm. Zhou et al., [26] detected that infection by *Toxoplasma* in human infertile couples was more than that in fertile couples. It might be associated with antibodies as anti-sperm in which being more in couples infected. Recently, a study on infection of *T. gondii* in males along sterility mentioned some of them were serologically IgM, CAg, and *Toxoplasma*-IgG, positive. Infection of *T. gondii* might effects fertility of men. [27] Lu et al. proposed that acute *T. gondii* infection may lead to male sterility, where Sun et al. [28] proposed that *T. gondii* acute infection may devastating experimentally the infected male mice reproductive function. Researchers utilized rats for studying toxoplasmosis effect on reproduction of males and observed that in group of *Toxoplasma*-infected, motility of sperms was significantly declined. Nevertheless, in median concentration of sperms, it was not find any differences of significant in controls and animals infected. Results show that a correlation possibly between disturbed reproduction and toxoplasmosis in males of rats. [29].

2.5 infertility and infection related to virus of human papilloma

Human virus papilloma prevalence estimation was globally at almost 12% in 2012, [30, 31] although HPV vaccines licensure more than 50% of localities. More than hundred HPV kinds might spread via

contact of skin-to-skin; include oral sex, sexual intercourse, and various contacts, such as genitals and surfaces of skin. Humans are susceptible mostly to such virus distributing in membranes of mucous and skin. It was estimated that higher than 50% populations being sexually active will be infected by HPV throughout their life, [32] and the infection risk elevates along condom use lack, sexual partners number along smoking [33]. Sexual majority being adults active might acquire possibly HPV throughout their life. In general, by elevating lifetime amount as sexual partners, developing illness risk reasoned to HPV elevates. [34] Human virus of papilloma 238 affecting infertility and infections of genital is regarded as commonly sexually viruses transmitted influencing fertility.

HPV is a pathogen type inducing chronic infections with no symptoms being specific. Generally, it is accepted which sexually viruses transmitted may make some infertility changes. Accordingly, there are some HPV effects on parameters of sperms. E.g., infections of HPV may alter motility of sperms. However, HPV might enhance fragmentation of sperm DNA and modify pH of semen. Generally, studies mention that infection by HPV is adverse factor influencing fertility of male or even resulting in sterility. Studies those reporting on sperm quality differences in between infected/uninfected men are discordant. Studies *in vitro* have showed that following incubation with certain HRHPV DNA, more normal motility of spermatozoa was observed. [35] Moreover, there are different seminal HPV influences on some parameters of sperms; some studies showed that in men infected by HPV, motility of sperm declined, but no information significantly provided on which parameter of sperm indicating infection of HPV. Nevertheless, no difference of significant was available in quality of sperms between men infected by HPV and men uninfected. It was suggested that HPV presence might not influence quality of sperm. Recently, three hundred samples of semen of couples IVF treated were checked for infection of DNA of HR-HPV. [35] Among uninfected and infected men, DNA HPV infection of no significant differences. In other words, quality of sperms does not influenced via HPV presence.

2.6 Infertility and infection related to virus of herpes simplex (HSV):

HSV may be classified into 2 kinds: HSV-1 and HSV-2. By contact as direct along viral shedding sites or along fluids of mucocutaneous virus carrying, people may contract HSV-1. HSV-1, mostly viruses prevalent among viruses of herpes, is transmitted via sores or secretions being oral, leading to manifestations being oral and ocular. [36]

Few reports have demonstrated the correlation between infection by HSV and infertility of male. Throughout analysis of semen, researchers compared sperms mean count and samples morphology. Utilizing method of real-time PCR, where HSV DNA prevalence in semen was observed. [37]. HSV is targeting system of reproduction, in which females and males infection cause problems of infertility; mechanism looks vary in the 2 populations. As illustrated in mice as transgenic and in few experiments, it looks to influence male's semen. [38] There was no certain semen parameters correlated along infection of HSV. [39].

2.7 infertility and infection in relation to semen of Bacteria

About 15% of male infertility situations might explain through infections about tract of genitor. [40] Male inflammation and infections in system of reproductively might impair cell of sperm, its function, and overall process of spermatogenic, [41] sperm alteration quantitative and qualitative.

A sperm contamination bacterium is highly normal and may cause semen quality impairment in sterile patients. Some reports mentioned the bacterial semen infection influence in fertility of male, where putative bacterial influence on quality of semen is inconsistent still. [42] Bacteria may influence directly the function of male reproduction system via acrosome reaction reduction leading to motile sperm agglutination, and cell morphology changing, and indirectly via synthesizing ROS resulting from bacterial infection inflammatory response. [43] Such bacterial negative influence motility of sperm is well-known. [44] Moretti et al. [45] showed that for whole groups just in 2, motility of sperms was significantly minimized. Moretti et al. proposed that bacterial existence may

possibly modify quality of sperms. For group as positive, the mean concentration sperms for bacteria were less significantly compared to controls, while for WHO, the value was considered always as normal. Some reports [42] mention that *Ureaplasma urealyticum*, *E. coli*, and *Enterococcus faecalis* were of negative effect on infertile patient's semen quality. Frequent alterations was noticed for spermatozoa due to bacteria in *in vivo* and *in vitro* cases are reduced concentration of sperms, alterations of sperm morphologically, motility loss, and impaired reactions of acrosome.

2.8 Human immunodeficiency virus

Along appearance and particularly the pandemic immune-deficiency syndrome development, virus's sexual transmission attention in human individuals and their health influences has accordingly peaked. [46] HIV leads to AIDS are enormously mostly studied among viruses transmitted sexually. Few studies detected HIV infection influence on parameters of sperm in men of positive HIV. Reports analyzed the correlation between HIV infection markers and semen characteristics. E.g., correlation of significant was observed between count of sperms and CD4 count cell. For fertile male, volume of semen for men of positive HIV, motility of sperms, and total count of sperms had been impaired. Dulioust *et al.* [47] reported about two hundreds men infected by HIV were free from symptoms of AIDS on characteristics of semen. Method as standardized was utilized for analyze collected samples of semen. Nevertheless, no relation was noticed between infection by HIV and characteristics of semen. It was reported in men infected by HIV, changes in semen might not enough remarkable for great influence fecundity. larger patient size perfect design of study is cohort longitudinal study, that prescribes parameters of semen through HIV infection development. [48].

2.9: Corona Virus infection and male fertility:

Virus of Corona causes infection for respiratory system include cold, pneumonia, coughing and sneezing whereas for animal it leads to diarrhea and diseases of upper respiratory. Virus of Corona transmitted through droplets as airborne from human to animal or human to human, entering cell of human via membrane receptor ACE-2 exopeptidase, ECDC and WHO suggested avoiding contact being close and place being public to infected individuals and animals pet [49]. Damage being testicular as possible theoretically was proposed and infertility subsequently associated after infection by COVID-19. Testicular damage possibility is caused either directly by viral invasion via SARS-COV2 virus binding to receptors of ACE2 or secondary to inflammatory and immunological response [49].

Diagnostic evaluation

Analysis of ejaculation

Physical examination and medical history are considered as assessments being standard for all males, include ultrasound of scrotal (US) [50] and analysis of semen. A rological and comprehensive examination is mentioned when analysis of semen reveals abnormalities in comparison to values being reference (Table 1).

Semen analysis frequency

When results of analysis of semen are normal based on WHO features, one test only is enough. When results are abnormal in 2 tests at least, more andrological detection is needed. It is significant to distinguish between the follows items:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% motile progressive spermatozoa;
- teratozoospermia: < 4% forms being normal.

Normal result of seminal analysis (WHO2000)	
Volume of semen (mL) 1.5 (1.4-1.7)	
Total number of sperms (10^6 /ejaculate) 39 (33-46)	Concentration of sperms (10^6 /mL) 15 (12-16)
Motility as total (PR + NP) 40 (38-42)	Motility as progressive (PR, %) 32 (31-34)
Vitality (spermatozoa being live, %) 58 (55-63)	Morphology of sperm (forms being normal, %) 4 (3.0-4.0)
Other threshold consensus values	pH > 7.2
Peroxidase ⁺ leukocytes (10^6 /mL) < 1.0	Investigations being optional
Test of MAR (spermatozoa being motile along particles being bound, %) < 50	Test of Immunobead (spermatozoa being motile along beads being bound, %) < 50
Seminal Zn (μ mol/ejaculate) > 2.4	Seminal fructose (μ mol/ejaculate) > 13
neutral seminal glucosidase (mU/ejaculate) < 20	
Parameter Lower limit reference (range)	Volume of semen (mL) 1.5 (1.4-1.7)
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Seminal Zn (μ mol/ejaculate) > 2.4	Seminal fructose (μ mol/ejaculate) > 13

Findings of Microbiology

Following bladder and urethritis exclusion of infection, $>10^6$ peroxidase⁺ WBC/ ml of ejaculate mention process of inflammation. At such case, culture must be done for common pathogens of urinary tract. A concentration of $>10^3$ cfu/mL pathogens of urinary tract in t ejaculate is an indication of bacteriospermia being significant. Time of sampling can affect the positive microorganism's rate for semen and the different strains isolation frequency [51]. Test as diagnostic ideal for semen *C. trachomatis* has not established yet [52].

In contrary to serological women findings, tests of antibody for *C. trachomatis* in plasma of semine are of no indication when no kind-certain methods are utilized [190]. Ureaplasma urealyticum is pathogenic only in high concentrations ($>10^3$ cfu/mL ejaculate). No more than 10% of analyzed samples for plasma of urea exceed such concentration [53]. Normal urethra colonization hampers the mycoplasma-associated clarification of urogenital infections, utilizing samples i.e., the ejaculate [54].

White blood cells

Clinical significance increased leukocytes concentration in ejaculate is so controversial [55]. Infection is indicating only via an increased leukocytes level. Despite leukocytospermia is an inflammation sign, it is not associated necessarily with viral or bacterial infections [56]. Based on WHO categorization, leukocytospermia is considered as $>10^6$ WBCs/mL. Only 2 studies have analyzed WBCs alterations of in patients ejaculate with confirmed prostates [57]. Both studies detected more leukocytes in males with prostates in comparison to those of no inflammation (CPPS, type NIH 3B).

Quality of sperm

Chronic prostates deleterious effects on density of sperm, morphology and motility are debatable issue [58]. Most reports are of contradictory results, and not yet prove that a prostitute being chronic has a significant duty in alteration of semen conventional parameters [59].

Alterations of seminal plasma

Seminal elastase plasma is an ejaculate biochemical polymorphonuclear indicator of lymphocyte activity [60], with a suggested approximately 600 ng/mL cut-off level [61]. Different cytokines are of inflammation involvement and may affect function of sperms. Many studies have proved the correlation between interleukin (IL) concentration, function of sperms and leukocytes, [62] where no associations were detected. Prostate considered as the IL-8 and IL-6 origin basic site in the seminal plasma. Cytokines, particularly IL-6, have significant function in inflammatory process of accessory male gland [63]. Nevertheless, increased levels of cytokine do not rely on leukocytes number in expressed secretion of prostate (EPS) [64].

Dysfunction of glandular secretory

Sex glands infections may impair their function being excretory. Declined amounts of phosphatase, citric acid, Zn, fructose, and a-glutamyl-transferase activity are disturbed parameters prostatic secretory indicators [58]. Declined concentration of fructose mentions impaired function of vesicular [65].

ROS

ROS may be elevated in infections of chronic urogenital correlated with elevated numbers of leukocyte [66]. Nevertheless, their significance biologically in prostates stays unclear [58].

Disease management

Chronic prostatitis treatment is normally targeted at symptoms being relieving [67]. The therapy aims for semen altered composition in men adnexitis are:

- Microorganisms eradication or reduction in prostatic semen and secretions;
- Inflammatory normalization secretory and leukocytes parameters;
- Sperm parameters improvement to counteract fertility [68].

Only (NIH II) being chronic bacterial prostate antibiotic therapy has provided relief symptomatically, microorganism's eradication, and a decline in humeral and cellular inflammatory parameters in secretions as urogenital. Despite antibiotics may improve quality of sperm [68], no evidence yet show that chronic prostate treatment elevates the conception probability [69].

Conclusion:

It had been concluded, infection of seminal fluid by virus, bacteria and different microorganism maybe interfere with male infertility problems through multiple pathological strategies. These organisms, which may cause impairing of semen parameters of total sperms count, motility or morphology. In addition to, the semen plasma had been estimated with significant positive correlation of low TAOC levels (oxidative defense system) and significant negative correlation of high 8-OHdG levels (oxidative stress status) regarding to sperm parameters that maybe induced sperms DNA damage. On the other hand, a significant detection role of immunological parameters changes by detecting of IL-10 and IFN- α in seminal plasma of infertile patients that may contribute with viral-IgGs and oxidative-antioxidants system in the male infertility as a co-factors. Finally, the assessment of all the above parameters, together with spermogram may play a significant role in male infertility treatment and diagnosis.

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