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Effect Of Antibiotic Therapy On Sperm Quality

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Abstract: Human semen contains the nutritious elements for the nourishment of the sperm. Semen being a sterile and nutritious fluid is very much suitable for the growth of bacteria. Semen gets contaminated by bacteria while sharing the same pathway as urine. Most commonly pathogens residing in the urinary tract and on the skin or urethra are most likely to contaminate the semen. Bacterial contamination of semen can affect sperm quality and still, research is going on to find out how bacteria is affecting sperm quality. The present review is divided into different thoughts i.e. there is evidence of bacteria affecting the sperm quality adversely and there is also evidence of no effect of bacteria in semen on sperm quality. Bacterial infections of the urogenital tract are usually treated with antibiotic therapy. Antibiotic therapy helps to remove the deleterious effects of bacteriospermia on sperm parameters but some researchers found out that antibiotics adversely affect the sperm. Most of the antibiotics used to treat the urogenital tract infection affect sperm motility, sperm viability, and sperm DNA integrity directly or indirectly.

Introduction

Human semen is very much prone to bacterial contamination and other microbes residing in the urogenital tract can affect the biological properties of semen. Semen is theoretically a sterile fluid but it gets infected by the pathogens of the urogenital tract or due to cross-contamination at the time of collection of semen for examination.

Human semen is a highly nutritious fluid, which makes it suitable medium for the growth of bacteria and other microorganisms. Semen has its microbiota. which contains the bacteria found on the skin, urinary tract and pathogenic bacteria in case of urogenital tract infections. Urogenital tract infection (UTI) is one of the significant cause infertility in males, interfering the whole process of spermatogenesis as well as sperm function [1]. The presence of bacteria in semen is known as Bacteriospermia and it can affect sperm function.

Human semen contains the male gamete, Sperm and it has a basic, but complex structure. Sperm play a key role in carrying the genetic information from the male body to female body to the oocyte and then transferring the genetic material into female gamete by penetrating it, the phenomenon is known as fertilization where fusion of both the gametes sperm and oocyte happens and an embryo is formed which carries the traits from both parents.. Human semen is the carrier of sperm and its role is to keep the sperm nourished and alive so that it can reach the oocyte for fertilization. Human semen is comprised of sperm (from the testis), secretions from seminal vesicles that contain fructose as a sugar source and amino acids, prostate secretions that contain proteolytic enzymes and secretions from bulbourethral glands. Human sperm has a very basic structure i.e. head, mid-piece and tail and these three parts have its role to play in the whole process of gamete transportation and fertilization. Sperm motility depends on the movement of tail and energy from mid-piece where sperm mitochondria is, oocyte penetration by sperm depends on the front portion of the head known as acrosome which contains the enzyme to penetrate the membrane of the oocyte, mid-

portion of the sperm head contains chromatin and it is very much prone to fragmentation because of intrinsic and extrinsic factors and sperm mid contains the mitochondria which is necessary for the survival and function of sperm. There are various studies which showed that bacterial presence in the semen affect the sperm quality in numerous ways which can cause detrimental effect in spermatogenesis, impediment of the seminal tract and blemishing the spermatozoa function [2], initiating the clumping of motile sperm, reduce the ability of acrosome reaction and producing the alterations in cell morphology and the produce the reactive oxygen species produced by the inflammatory response against the bacterial infection [3]. Some bacteria produce a specific kind of protein that affects sperm motility directly. Prabha *et al.* in 2009 showed that *Staphylococcus aureus* produced a protein named as Sperm Immobilization Factor (SIF) that affected the sperm motility and vitality directly [4]. Also this bacteria is found in both gender's genital tracts. Some studies also suggested that bacteria induce apoptosis in spermatozoa by increasing the externalization of Phosphatidylserine (PS), a lipid present in the sperm membrane and externalization of PS is considered as the first step of apoptosis in sperm. [5]. Apoptosis does not involve exogenous Reactive Oxygen Species (ROS) and may cause alternation in the motility, vitality and DNA integrity of spermatozoa in male accessory gland infections (MAGI). DNA fragmentation induced by bacterial infection of semen may lead to serious consequences like infertility, miscarriages and birth defects in the offspring. The bacterial infections lead to premature emergence of histones. In mammals, reduced levels of histone correlate with impaired fertility. Many researchers found that different bacterial species can affect sperm DNA integrity, for example, *C. trachomatis, U. urealyticum, Mycoplasma* spps [6]. Fraczek *et al.* (2015) studied the mechanism of bacterial infections affecting the sperm [7]

The effect of the presence of bacteria on the sperm parameters is still being not fully explored by researchers. There are two schools of thought on the issue, one set of researchers [8-9] states that presence of bacteria in semen is merely contamination and it doesn't affect the sperm but the other of the set of people differ completely [1-6]. The purpose of this review is not to debate about that, there is a more practical concern related to bacteriospermia which needs to be addressed and researched with a more comprehensive perspective. To detect bacteriospermia the clinician relies on a thorough semen analysis report followed by bacteriological culture of semen. In semen analysis, if the number of leukocytes is more than 1×10^6, that is called as leukocytospermia [10]. Leukocytospermia reflects that there is some infection in the urogenital tract, after this the patient is prescribed with preliminary antibiotic therapy and to confirm that infection bacteriological investigation of semen is done and a confirmed diagnosis of bacterial investigation is made after that patient is prescribed with antibiotics as per the culture sensitivity report. Sometimes if the semen analysis is not done properly and the investigator is not able to differentiate between the leukocytes and immature spermatids because both the cells look similar in wet mount preparations [11], a false diagnosis of leukocytospermia is made and the patient is prescribed with antibiotic therapy. In both cases, antibiotics of various classes are used to treat the leukocytospermia. This article aims to study the effect of commonly used antibiotics to treat urogenital infections on sperm parameters by doing the research review. Studies showing the interaction between antibiotics and sperm parameters are included in this review. We are only including the drugs used to treat bacterial infections, drug classes like anthelmintic, anti-fungal, anti-viral, etc. are not discussed in this manuscript. In 1991, Schlegel *et al.* published a review in Fertility and Sterility and study the antibiotics effect on on male fertility [12].

Antibiotic effect on male fertility

The harmful effects of antibiotics on spermatogenesis or sperm function have been demonstrated throughout the animal kingdom. The effects of antibiotics on fertility and the implications for the management of the infertile couple may be larger than commonly presented. In 1957 W. Nelson & R. Bunge did a study about the effect of nitrofurantoin on spermatogenesis in humans. Nitrofurantoin is the most common antibiotic used to treat urinary tract infections as well as infections of the genital tract. They gave 10 mg/kg of nitrofurantoin to 36 young healthy white males daily. It was observed that under certain unpredictable instances nitrofurantoin caused slightly to moderate spermatogenic arrest temporarily. Study showed that 23 individuals significantly observe changes in testicular biopsies or sperm counts out of 36 volunteers study who took the antibiotic for 14 days, around 13 showed a partially decrease in the sperm counts and 6 individuals showed no changes in the testicular biopsies. The incidence of arrest is even less likely to occur with the lower clinical doses as in current use, and they suggested that drugs may significantly interference with fertility [13].

This was one of the initial studies conducted to study the adverse effects of antibiotics on male fertility. The germinal epithelium is the most multiplying tissue and it produces millions of sperms every hour. It is a very sensitive tissue and regulation of spermatogenesis & testicular function is a very complex process, so because of that chemicals and drugs are very likely to interfere with the process and might even lead to infertility. There are drugs and chemicals which hinder the testosterone synthesis directly or indirectly. They may inhibit the effect of testosterone to target organs, which may lead to interference with the process of sperm maturation and the function of other sexual glands [14].

There are several studies conducted on animal models to study the effect of different antibiotics on male fertility. Manson *et al.* (1987) studied the effect of cefonicid and other cephalosporins on the sexual development of male rats. The purpose of their study was to determine the effect of cefonicid (a type of cephalosporin antibiotics) with a modified *N*-methylthiotetrazome (MTT) side chain ontesticular toxicity in male rats. Rats aging from 6-36 days postpartum administered with 50-1000 mg/kg daily with the cefonicid antibiotic. For positive control, Moxalactam antibiotic is used because it also contains the *N*-methylthiotetrazome (MTT) side chain and for the negative control, Cephalothin antibiotic is used which lacks the *N*-methylthiotetrazome (MTT) side chain with the same dose respectively. Moxalactam caused a significant reduction in testicular and seminal vesicle weight of 37 days old rats and histological examination revealed damage of the seminiferous tubules at all dose levels but they didn't found any significant damage caused by cefonicid in the same age group. More research concerning different age groups is required to conclude because cephalosporins are used very frequently [15].

There are more studies on animal models which states that antibiotics affect adversely. Fluoroquinolones, a class of commonly recommended antibiotic for the medication of genitourinary tract infections. Khaki *et al.* (2008) studied the effect of ciprofloxacin on testis apoptosis and sperm parameters viz. sperm concentration, motility, and viability. Ciprofloxacin is absorbed orally and its mechanism of action on bacteria is inhibiting the DNA gyrase of the bacterial cell. Animal study was conducted on 20 rats having both control and experimental groups. Furthermore, the control was administrated with just food and water and the experimental group is supplemented with 12.5 mg/kg of ciprofloxacin orally for 60 days. Rats were sacrificed the cauda epididymis is removed to study sperm parameters and testis tissue is prepared for TUNEL assay to study apoptosis. It was found out that the number of apoptotic germ cells were more in the experimental group seminiferous tubules than the control group. Sperm concentration, motility, and viability were significantly lower in the experimental group [16]. One of the reasons that can explain this effect could be

that ciprofloxacin hinders the ATP production essential for vitality and motility of sperm cells [17] and the apoptosis. The reason could be the rise in peroxide radical generation in testis by ciprofloxacin [18]. A similar type of study was done by El-Harouny *et al.* (2009) with ofloxacin, which belongs to same class of fluoroquinolone. They divided rats into two main groups A & B, from where group A was subdivided into A1 which received a low dosage (72 mg/kg) for 14 days and A2 which received a high dosage (400 mg/kg) for 14 days. Group B was also subdivided into two groups B1 (low dosage for 28 days) and B2 (High dosage for 28 days). It was concluded by the researcher that ofloxacin has a detrimental effect on the testis of rats and the long term use of the drug causes more damage [19].

Fahmy *et al.* (2017) studied the effect of Amoxicillin-clavulanic acid antibiotic on sperm. They stated that the use of Amoxicillin-clavulanic acid antibiotic can induce sperm abnormalities and histopathological changes in the liver, kidney, testis, brain, and heart of mice. Amoxicillin-clavulanic acid antibiotic is a widely prescribed broad-spectrum drug for infections like urinary tract infections, pneumonia, bacterial bronchitis, sinusitis, ear, and skin infections. Its mechanism of action is inhibiting the formation of the bacterial cell wall. It was reported that it induces the production of reactive oxygen species (ROS) and the effect of ROS on spermatogenesis is well known. So, treatment with Amoxicillin-clavulanic acid antibiotic induces sperm morphological abnormalities as well as histopathological changes in different body organs [20].

To study this phenomenon in humans some researchers try to understand the effect of antibiotics on sperm *in-vitro*. King *et al.* (1997) studied the effect of amoxicillin, ofloxacin, ciprofloxacin hydrochloride, nitrofurantoin monohydrate, doxycycline hyclate, cefuroxime axetil on cryopreserved-thawed sperm. They found out that ciprofloxacin affects hyperactivation of sperm by altering the sperm membrane, ofloxacin didn't cause any harm to the sperm, in fact, it significantly improved the sperm fertilization capacity, nitrofurantoin decreased the sperm motility and fertilizing capacity, cefuroxime affected sperm motility, amoxicillin also affected the motility and doxycycline affected the sperm capacitation process [21]. Similar kind of experiment was done by Hargreves *et al.* (1998) with fresh semen sample and different antibiotics viz. co-trimoxazole, erythromycin, amoxicillin, tetracycline, and chloroquine and they found out that tetracycline at a concentration as low as 2.5 mg/ml can cause inhibition of sperm motility and at a dose of 50 mg/ml all spermatozoa became immotile. Erythromycin also affected the motility. Amoxicillin did not affect sperm movement though it affected sperm viability at high dosage. Co-trimaxazole did not affect the sperm movement at low concentration but at 500 mg/ml concentration it reduced the movement by 34%. Chloroquine did not cause any harm to the sperm [22].

The role of antibiotics can never be disregarded in modern-day health care as well as lifestyle. Antibiotics are necessary to treat urogenital tract infections. These infections are considered as one of the factors interfering with the fertility potential of males. One of the most prescribed antibiotics to males in the case of leukocytospermia is Doxycycline. Leukocytospermia has a deleterious effect on male fertility and antibiotic therapy for such a condition might improve the male fecundity. Hamada *et al.* in 2011 did a retrospective analysis of patients attending their fertility clinic from September 2006 to February 2008. They made two groups of patients one with leukocytopsermia and another control group without leukocytopsermia. Since September 2006 the centrr had the practice to treat the men with leukocytopsermia using a 3-week course of doxycycline 100mg orally twice a day. They found out that patients who got doxycycline therapy had slightly better sperm parameters after treatment [23-26].

Limitation of work

Antibiotic therapies are increasingly used in present-day healthcare, especially a patient visiting fertility clinic is prescribed with empirical antibiotic therapy to cut the risk of urogenital infections interfering with the fertility treatment. Antibiotics are used very normally in present-day lifestyle maybe because they are easily available, but this leads to antibiotic misuse or one can say antibiotic abuse. There are several studies mentioned in this paper that show how antibiotics can affect the male fertility potential by affecting the spermatogenesis and directly or indirectly affecting the sperm. But still, there is more evidence required to find out about the harmful effects of antibiotics on sperm and male fertility potential. There are so many classes of antibiotics which need to be studied yet, for effective doses and toxicity for sperm and at the same time it will be suitable to perform its function, how their adverse effect can be avoided.

Conclusion

Human semen is full of nourishing constituents which makes it suitable for the growth of bacteria. It can get contaminated by normal skin flora as well as pathogenic bacteria. Research suggests that the presence of bacteria in semen can interfere with sperm quality[1-3]. The presence of bacteria in semen leads to the occurrence of leukocytes as a response toward the infections, and these leukocytes are not good for sperm because they produce oxidative stress which may cause sperm DNA fragmentation as well as apoptosis [5-7]. To treat infections of the urogenital tract and leukocytospermia clinicians prescribe various antibiotics but there are studies which state that antibiotics used to treat infections cause adverse effects on sperm parameter as well as male fertility potential. Various research studies were conducted on animal models, cryopreserved-thawed semen samples, and human models but still, no significant conclusion was achieved. Some studies suggested that there is no effect of antibiotic therapy on sperm parameters, some suggested that antibiotic therapy helped in improving sperm quality by treating the infection and some suggested that antibiotics negatively affected sperm quality. Still, there is a lot to know about the interaction between sperm and different classes of antibiotics.

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