Antioxidants, anti-inflammatory drugs and antibiotics in the treatment of reproductive tract infections and their association with male infertility

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ABSTRACT

Male infertility is a multifactorial condition which in some cases are presented with unidentifiable underlying causes. Men with idiopathic or non-curable oligoasthenoteratozoospermia as well as with unexplained infertility may be provided with non-hormonal medical treatment which includes the use of anti-inflammatory, antioxidants, fibrinolytic compounds, vitamin supplementation, and oligo-elements, presuming that most of these cases are possibly caused by inflammation and/or oxidative stress. In the case of the known pathogenic mechanisms responsible for male infertility, the treatments include specific antibiotics targeting the exact pathogenic strains, anti-inflammatory drugs targeting particular infections, as well as the use of antioxidants, singly or in combinations to ameliorate the detected oxidative stress. Combined non-hormonal therapies have also shown to improve semen quality. Since there is a lack of consensus regarding the exact dose, duration and effects of non-hormonal treatment on male infertility, this review article aims to present a comprehensive summary of how antioxidants, anti-inflammatory drugs and antibiotics treatment in reproductive tract infections are associated with amelioration of male fertility parameters.

Keywords: antibiotics, anti-inflammatory, antioxidants, male infertility, semen quality.

INTRODUCTION

Male infertility comprises of a complex etiopathology with innumerable possible causes for its occurrence.1 In majority of male infertility cases, they may be idiopathic and in some, they may also remain unexplained.1-6

In these cases, due to lack of clarity in identifying the cause of fertility problems, direct hormonal treatments may not provide desired outcome and require intervention of non-hormonal medical treatments. These include use of antioxidants, anti-inflammatory agents as well as antibiotics in an attempt to solve the possible cause(s) of male infertility.7 Studies show that such non-hormonal medical treatment lead to significant improvement in semen parameters and aid sperm production and maturation rendering a healthy microenvironment.8,9

Treatment of men with idiopathic oligoasthenoteratozoospermia (OAT), non-curable disease-induced OAT, and with unexplained male infertility, rely on prediction of the underlying causes which may mostly be inflammation or oxidative stress (OS).10,11 Fibrinolytic agents, anti-inflammatory, antioxidant compounds, and vitamin supplementation have shown to improve fertility parameters in some of these cases, but further studies are required in this
Antioxidants treatment, either with single antioxidant type or in combinations, have been shown to be beneficial in case of idiopathic male infertility. Very often, couple with male factor infertility are suggested to undergo assisted reproduction techniques (ART), after antioxidant therapy.

In some male infertility cases the exact causatives can be specifically identified, whether they are infections, inflammation, and/or increased OS, besides the endocrine causes. Treatment in such cases include drugs that target the exact cause elements. For example, male infertility due to urogenital tract infections, are mainly treated with specific antibiotics targeting the eradication of the identified microorganisms involved.

Reports on the effectiveness of antioxidants, anti-inflammatory drugs and antibiotics in the treatment of reproductive tract infections are not adequate to meet consensus regarding the exact dose and duration of treatment. Thus, the present review article provides a precise conception on the association of such non-hormonal treatment with changes in male reproductive functions, in order to encourage further studies addressing treatment and management of idiopathic, unexplained and/or non-endocrine factors-induced male infertility.

**Antioxidants used in the treatment of Reproductive Tract Infection and their association with Male Infertility**

Idiopathic male infertility accounts for more than 25% of overall male infertility cases. Oxidative stress (OS) is a major underlying causative of idiopathic male infertility contributing to 30-80% of cases. It is a pathological state that is induced by excessive generation of reactive oxygen species (ROS) that exceeds the physiological levels. Endogenous antioxidants maintain the seminal redox balance by scavenging excess ROS and disruption between the intricate balance between these reductants and oxidants may lead to OS.

Endogenous antioxidants can be enzymatic, such as catalase, superoxide dismutase (SOD), thiol peroxidase, and non-enzymatic such as the glutathione. When the levels of seminal plasma ROS overwhelms the endogenous antioxidant capacity, seminal parameters may get adversely affected. This may explain why antioxidants find huge relevance in the treatment and management of idiopathic male infertility. In such cases, exogenous antioxidants may be obtained through diet or as supplements. These include micronutrients such as vitamin A, vitamin C, vitamin E, carnitines, lycopene and trace elements like zinc and selenium. The present review overviews functions of some mostly used antioxidants as the treatments of male infertility besides discussing the key endogenous antioxidant enzymes.

**Superoxide Dismutases (SOD)**

SODs are endogenous metalloenzymes that act for the conversion of superoxide to hydrogen peroxide (H₂O₂). SODs comprise of one extracellular and two intracellular forms. In the active center the intracellular form contains copper and zinc (CuZnSOD) and is encoded by the SOD1 gene. It is generally present in the cytoplasm, while the enzymes with manganese (MnSOD) operates in mitochondrial matrix. The gene SOD2 is induced by inflammatory responses mainly through the activation of the nuclear factor kappa B (NF-κB). Homozygous SOD2 gene-deficient mice have severe heart damage and die shortly after birth. In these mice, there have been no defects in the genital tract. In comparison, transgenic male mice with higher MnSOD levels are infertile.

Erectile function has been shown to be enhanced by the transfer of the SOD3 gene into the penis in older rats. Scavenging superoxide increases the half-life of nitric oxide, leading to higher cGMP levels. CuZnSOD (75%) and ECSOD (25%), which most probably originate from prostate, are the main active isoenzymes in seminal plasma. SODs were shown to have a role in protecting testicular cells from in vivo and in vitro heat stress-induced apoptosis. Furthermore, SOD activities have been demonstrated to be significantly lower in infertile men as compared to the fertile control subjects, and it positively correlates with sperm morphology and motility.

There are in vitro studies indicating that SODs can contribute to sperm improvements in thawed semen samples. Supplementation with a SOD mimetic agent, MnTE (manganese (III) mesotetrakis), showed to increase total sperm motility, membrane integrity, and viability of goat semen samples after thawing, the acrosomal integrity and the blastocyst formation rate. However, the degree of improved sperm parameters is greater when simultaneous catalases are added as the SOD mimetics protected only against superoxide, but not H₂O₂.

There is evidence that SODs are also beneficial for human spermatozoa. At a dose of 400U/mL, exogenous SODs could prevent loss of sperm motility in human. Some commonly male fertility enhancer products that also contain other anti-oxidants (such as zinc, and folic acid) include SOD. Though there is scarcity of reports suggesting exact dosage oral SOD supplementation for human sperm, a dose 150UI/day for at least three months is generally practiced.

**Catalase**

Catalase is an extracellular heme enzyme with a central iron atom and is produced by the prostate. It acts to catalyze the breakdown of the reactive H₂O₂ into neutral molecules, oxygen (O₂) and water (H₂O). The sperm and seminal plasma of both humans and rats have demonstrated its presence. Catalase also possess the physiological role in nitric oxide-mediated capacitation of spermatozoa. Since H₂O₂ has a significant role in sperm motility, its dissociation by catalase has been shown to adversely impact sperm quality. In fact, certain level of seminal H₂O₂ helps to enhance sperm membrane fluidity that is essential for sperm-oocyte fusion. This may be the reason why catalase is not available commercially.

**Glutathione Peroxidase (GPxs)**

GPxs act to mitigate hydrogen peroxide as well as organic peroxides (that also include phospholipids) by donation of electron via the reduced form of glutathione (GSH). Sperm DNA is protected against oxidative damage by GPX which plays a role mainly in mitochondrial chromatin condensation. Impaired expressions of GPX are reportedly associated with...
oligoasthenoteratozoospermia in human spermatozoa. GPXs are divided by the selenocysteine in an enzyme isoform into two groups. As selenium deficiency may lead to male infertility, GPXs that contain selenium supposedly are candidates for the faulty molecule. Minimum four isoenzymes in mammals pertain to the GPX that contains selenium. The cytosolic isoform, GPX1, is extensively expressed in various tissues and, acts to inhibit apoptosis initiated by noxious stimuli like oxidative stress. However, GPX1 knockout mouse does not display any abnormality in reproduction. GPX2 and GPX3 are isoforms expressed in the gastrointestinal and the plasma, respectively. The isoform, GPX4 has been found to be highly expressed in testes. It comprises about 50% of the capsule content that incorporates the helix of mitochondria into the mid piece of sperm. Mice with GPX4 gene knockout show early embryonic death. It encodes for a protein that is particularly expressed in sperm nuclei and reportedly acts as protamine thiol peroxidase. GPX5 represents a non-selenium isoform specifically expressed in epididymis. Henceforth, it is secreted in the caput and lumen of caudal epididymis. Its activity as a peroxide scavenger is not very significant. However, GPXs are not yet applied in the clinical management of male infertility.

Glutathione: Glutathione is a tripeptide containing sulfur in both a reduced state (GSH) and an oxidative state (GSSG). GSH is active in maintaining the reduced state of the intracellular system and is also an electron donor to GPX. Through reconstituting protein thiol groups (-SH), the GSH demonstrates its antioxidant activity and prevents the lipid peroxidation of its cell membrane. GSH therapy has been shown to be beneficial on the sperm quality in animals. Species with asthenozoospermia due to varicocele and rabbits with dispermy due to cryptorchidism have been shown GSH-mediated improvement in sperm motility and fertilization. The reduction of glutathione in human seminal plasma results in sperm cellular instability, which leads to disorder in motility. It is been suggested to possess therapeutic value in certain reproductive diseases, specifically related to inflammatory conditions. GSH complementation to infertile men with urogenital tract inflammation leads to significant sperm parameters improvement such as sperm concentration, mobility, and morphology. It has a distinct protective role on cell membrane lipids. Glutathione at an intramuscular dose of 600mg/day for 2-3 months is standardized for the treatment of idiopathic infertility patients. However, may be owing to its low compliance, GSH is not widely used for male infertility treatment.

Coenzyme Q10 (CoQ10): CoQ10 is an essential antioxidant which is abundant in the sperm mitochondria. It plays vital roles in the cellular respiration and in energy production. Moreover, it also inhibits the production of superoxide ions to protect against OS mediated sperm damage. This explains the result obtained from the studies of Nadjarzadeh, Shidfar et al. where CoQ10 concentration positively correlates with normal sperm morphology and enzymatic enzyme concentrations. It is also evident that at least three-months of CoQ10 treatment at dose of 200-600mg/day, could improve semen parameters, antioxidant enzymes activities in idiopathic infertility patients.

Vitamins

Carotenoids are a bunch of fat-soluble natural compounds found basically in yellow, ruddy, orange, and pink vegetables. These retinoids are basically vitamin A precursors. The gastrointestinal tract is the site of production of retinal to its conversion to retinol, the most essential vitamin A component. Carotenoids are natural antioxidants, which protect the integrity of the cell membrane, control the proliferation of the epithelium cells and control spermatogenesis. Studies on rats show that retinoids have beneficial effects on fetal and neonatal Sertoli cells, Leydig cells as well as germ cells. Carotenoid dietary deficiency can lead to impaired sperm motility. Experiments on bulls have shown retinol can stabilize the sperm acrosomal membrane if the high temperature induces oxidative stress. Experiments on bulls have shown retinol can stabilize the sperm acrosomal membrane if the high temperature induces oxidative stress. Therefore, vitamin-A may be a therapeutic alternative for male infertility. There have been few studies assessing vitamin A effects on human sperm parameters.

Vitamin E, alone or in combination with other antioxidants at the dose of about 400 mg/day showed significant improvement in sperm concentration and progressive sperm motility in men with idiopathic infertility. Vitamin C is another essential antioxidant agent which is water-soluble and aid reactive radical reduction from varied sources. It also helps to recycle the oxidized vitamin E. However, effects of vitamins on total sperm motility and sperm DNA integrity need further interventions.

Omega-3 fatty acids: Omega-3 fatty acid is a proven antioxidant. As both the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) having high safety profiles, may be a potential nutritional supplementation to improve semen quality. A double-blind randomized study in the present article reflected that omega-3 fatty acid supplementation at the dosage of 1.84g per day for 32 weeks had beneficial impact on sperm concentration on infertile men with idiopathic OAT.

Carnitines: Carnitine has been associated with the source of energy in spermatozoa because of its presence in the epididymis where the immature spermatozoa goes through a phase of maturation. This L-carnitine is basically obtained from the plasma which is further transported to the epididymal cells. The presence of carnitine in epididymis is noted to be 10 folds higher as compared to other parts of the human body. Hence, carnitine can be used as one of the antioxidants for the improvement of the fertility parameters. However, it is found that the combination of L-carnitine with L- acetyl- carnitine can help increasing the quality if sperm when the baseline value of semen parameters are extremely low. The study by Busetto et al., shows that L-carnitine significantly improved sperm concentration in oligo-astheno-teratozoospermic men. Studies also have shown improvements in other semen parameters such as sperm count and motility.
Micronutrients
Micronutrients concentration including selenium, copper and zinc were found to have positive correlation with human sperm quality.40

Selenium: Selenium is an important micronutrient for normal development of the testes, sperm production and function. Deficiency of selenium has been correlated with seminiferous epithelium atrophy, spermatogenesis disorders, the sperm maturation in the epididymis, the reduction of the testicular volume, decreased motility of the sperm, and altered sperm morphology.41 It is still unclear how precisely selenium decreases or increases oxidative stress and sperm parameters. The actions of selenium are suggested to be mediated via selenoenzymes, such as GPXs.73 The standard dose of selenium ranges from 80 μg to 300μg per day for a minimum duration of three months.

Zinc: More than a couple of hundreds of important metabolic enzymes include zinc as a component. Thus, zinc participates in synthesis of proteins, nuclear acids, as well as in the process of cell division.40 It seems to regulate seminal oxidation processes and catalase-like activities in infertile men with asthenozoospermia.74 Zinc is administered orally, either alone or in addition to follic acid (5 mg daily) once or twice daily for three-to- four months at the 220 mg dose.62

Herbal medicines
Herbal medicines are in use male infertility treatment from ancient time and in recent decades these comprise one of the leading research areas.75 Herbal therapy include but not limited to Indian Ayurveda, traditional Chinese medicine, and Alternative Medicines as in the Western countries.76 For example, among the Chinese traditional medicines, Sheng Jing represents a mixture of fifteen herbs and reportedly has the potential to restore semen quality and endocrine parameters in infertile men with oligozoospermia.77 South African herbal therapy also cater to primary healthcare problems and certain reproductive issues.78 Typha capensis, also referred to as love reed is a Southern African plant with proven antioxidant properties and reportedly ameliorate Leydig cell steroidogenesis.79,80 In Ayurveda, various herbal mixtures are suggested to improve male fertility parameters. The most commonly used herbs are Mucuna pruriens (velvet bean), Withania somnifera (Indian ginseng), Tribulus terrestris (land caltrops), Glycyrrhiza glabra (licorice), Terminalia arjuna (Arjuna tree), Phyllanthus emblica (Indian gooseberry or amla), Piper longum (Indian long pepper) and Zingiber officinale (ginger).81,82 These popular therapeutic approach to cure male infertility need thorough research to properly implement for a holistic effect on men’s health.

Combination of antioxidants
The synergistic effects of various antioxidants have been investigated. It is evidenced that combination therapy of vitamin E (400mg) and selenium (225 μg) could significantly decrease lipid peroxidation and enhance sperm motility in three months treatment duration.89 Study in mouse model shows that coadministration of vitamin E (100mg/kg) and vitamin C(10mg/kg) could reduce testicular malonaldehyde content and improve sperm count decreasing the percentage of sperm with abnormal morphology.83 Moreover, a two-month therapy using combination of vitamin C (1g) and vitamin E (1g) also showed reduction in sperm DNA fragmentation in human84. In addition, this association led to an improvement in the clinical pregnancy and implantation rates compared to the group of patients receiving placebo.84 The combination of vitamin E and vitamin C significantly improves sperm kinetics and viability leading to improved fertility rate85, which may indicate their high therapeutic importance in the treatment of idiopathic male infertility.

Antioxidants and basic semen parameters
Antioxidant treatment have shown improvement in semen parameters in innumerable studies revealing significant increase in sperm concentration, sperm motility, vitality and morphology.86 In the present systematic review, the clinical trials include treatment of idiopathic male infertility with CoQ10, vitamin E, pentoxifylline, omega-3 fatty acid, Withania somnifera, and carnitines. In all the cases, antioxidant treatment is associated with improvements in semen parameters, mainly sperm concentration and total sperm motility, when given for the duration of 3 months or more.

Antioxidants on sperm DNA fragmentation
Sperm DNA fragmentation is one of the most important factors associated with male infertility.14, 87 Studies have shown that increased level of sperm DNA fragmentation can be associated with oxidative stress88. In addition, the study by Dorostghoal et al., shows that reduced antioxidant levels can serve as a biomarker for detecting higher DNA damage and poor semen parameters.89 Studies concerning antioxidant treatment in male infertility have shown beneficial impacts of various antioxidant on sperm DNA integrity and decreased sperm DNA fragmentation.90 A study by Salehi et al., shows that antioxidant therapy has the potential to improve the semen parameters as well as have significant positive effect on sperm chromatin integrity.91

Effect of Antibiotics on Male Infertility
Several antibiotics have been used in the management of male reproductive tract infections.92 The choice of antibiotics depends on the causative organism and the result of the culture and sensitivity.10,93 Mesbah et al.94 reported that the common microorganisms involved in sexually transmitted infections, that interfere with male fertility, are the Chlamydia trachomatis and Neisseria gonorrhoea.94 Sometimes, male infertility may be due to non-sexually transmitted epididymo-orchitis, mostly caused by Escherichia coli. Parvis and colleagues2 reported that aerobic gram-negative bacilli (E. coli) plays significant roles in non-gonococcal bacterial infections of the male genital tract leading to up to 20-30% of cases of acute epididymitis and many examples of chronic bacterial prostatitis-vesiculitis. Additionally, it was also noted that gram positive bacteria frequently colonize in the male urethra but are rarely a causative factor in non-gonococcal urethritis or acute epididymitis. Over almost two decades, two organisms, in particular, have been discussed as having critical roles in both symptomatic and...
asymptomatic infections in the male reproductive tract, and they are *Ureaplasma urealyticum* and *Chlamydia trachomatis*. Several studies have highlighted the effectiveness of antibiotics regimen in the treatment of RTIs and male accessory glands infections (MAGI)\(^{94-96}\). The choice of the antibiotic must depend on the nature of the detected micro-organism and the findings of the relative antibiogram, since a unique treatment is prescribed. There are a varied antibiotics classes that can be used in infection-induced fertility disorders. It should also be pointed out that most of these microorganisms can be transmitted sexually and sexual encounters must be avoided during medication and the female partners should also be monitored and treated for any infection if required.

**Cephalosporins:** Cephalosporins are type of beta-lactam antibiotics. They can be taken orally or intravenously. They are indicated for the prevention and treatment of most bacterial infections. The Centre for Disease Control and Prevention (CDC) in 2015\(^8\) recommend as first line, for the treatment of gonococcal urethritis, the use of Ceftriaxone 125mg intramuscular as a single dose and then as a second choice, the use of Ciprofloxacin 500mg orally or Ofloxacin 400mg orally or Levofloxacin 250mg orally as a single dose. Common side effects of cephalosporins include diarrhea, nausea, rash while about 10% of patients that receive it experience allergic hypersensitivity to penicillins and/or cephapenems.

**Macrolide (Azithromycin and Erythromycin):** As gonorrhea is often accompanied by Chlamydia infection, an antichlamydial active therapy should be added. First choice regimen in the treatment of Chlamydial infections is Azithromycin 1g orally as a single dose or Doxycyline 100mg twice daily orally for seven days and as second choice, the use of Erythromycin 500mg four times daily orally for seven days or Ofloxacin 500mg orally once a day for seven days. If the therapy fails, infections with *Trichomonas vaginalis* and Mycoplasma should be considered and treated with a combination of Metronidazole 2g orally as a single dose and Erythromycin 500mg orally four times daily for 7 days. Macrolides have been shown to be effective against mycoplasma and chlamydia and are a substitute for patients with a penicillin allergy. It also has good penetration to the prostatic tissues. The European Association of Urology (EAU)\(^8\) advocates the use of parenteral administration of high doses of bactericidal antibiotics in acute bacterial prostatitis. Such antibiotics as aminoglycoside and a penicillin derivative or a third-generation cephalosporin. In less severe situations, a fluoroquinolone may be given orally for at least ten days.

**Quinolones (Ofloxacin, Ciprofloxacin, Pefloxacin etc.):** In chronic bacterial prostatitis and inflammatory chronic pelvic pain syndrome (CPPS), a fluoroquinolone or trimethoprim should be given orally for two weeks at the first instance and then continued, after microbial culture, for 4 to 6 weeks. The first-choice drug therapy for epididymitis, orchitis should be fluoroquinolones, preferably those agents that react well against *Chlamydia trachomatis*, e.g. Ofloxacin and levofloxacin, because of their broad antibacterial spectra and favorable penetration into urogenital tissues. The quinolones have high volume of distribution and moderate to excellent bioavailability.

**Tetracycline (Doxycycline and Tetracycline):** In Italy, Vicari\(^8\) administered 122 patients with MAGI either ofloxacin or doxycycline for 14 consecutive days per month for three months. They found that the isolated bacterial strains exhibited a high susceptibility to both ofloxacin and doxycycline and that in terms of minimum inhibition concentration (MIC) values of the isolates, the random antibiotics (ofloxacin and doxycycline) chosen had lower MIC values (<1mg/l) than any of the other antimicrobials tested *in vitro*. Doxycycline is a first line drug for the treatment of non-gonococcal urethritis (due to ureaplasma) and other chlamydial infections. It is generally well tolerated and have very minor side effects (loose stool, nausea, vomiting and abdominal pains). Tetracycline, on the other hand is sparingly used for the treatment of male reproductive tract infections and when used causes discoloration of the teeth.

A meta-analysis of antibiotic treatment of male infertility in 2003\(^{99}\) noted that the most common group of antibiotics in the treatment of leukocytespermia is broad-spectrum antibiotics, which are not targeted towards specific bacteria. Therefore, even if there is no diagnosis of inflammation in the genital tract or pathological organisms isolated in leukocytespermic patients, broad-spectrum antibiotics should be given, and this has been found to reduce the somatic immune activity and lead to a reduction in the level of leukocytes in testes and epididymis thereby improving ejaculate quality.\(^{100}\)

**Others (Nitrofurantoin, Trimethoprin, Sulphamethoxazole):** Sometimes, male reproductive tract infections are preceded or predisposed by infections of the urinary tract, mainly because of their close anatomic relation. When this happens, especially when it is recurrent and uncomplicated, the American Society of Health Pharmacists recommends the use of Nitrofurantoin 50-100mg per day for seven days, though the length of treatment may vary.\(^{101}\) Trimethoprin-Sulphamethoxazole (TMP-SMX) 40/200 mg per day for one week can also be used.

**Associations of antibiotics treatment with male infertility:**

The result of associations between anti-bacterial therapy and infertility is conflicting in several studies.\(^{96}\) Whereas some obtained improvement in the semen quality and pregnancy rates, others have failed to achieve any success. The discrepancies may, however, be due to the heterogenous group of patients studied, anti-bacterial therapy may have been inadequate in terms of dosage and duration, and the WBC may persist even after antimicrobials in some patients affected by complicated MAGI, for example, prostatovesiculopelididymitidis.\(^{99}\)

A meta-analysis of Skau and Folstad\(^{86}\) revealed that there was a significant positive effect of antibiotic treatment for the following sperm parameters: sperm volume, sperm concentration, sperm motility and sperm morphology. Antibiotics treatment also significantly reduced the number of leukocytes in the ejaculates of male infertility patients. Thus, in general, males treated with antibiotics were relieved from leukocytespermia and produced ejaculates of higher quality.
Also, in Vicari’s study, when the bacteriological cure was obtained, 28.2% of the male patients treated with antimicrobials achieved spontaneous pregnancy which was statistically significant when compared with only 5.4% of the male patients not treated with antibiotics that also got pregnant.

However, a double-blind clinical trial by Comhaire et al. where he treated both partners of infertile couples, with evidence of MAGI, with doxycycline recorded no difference between the antibiotic treatment and placebo groups with regards to pregnancy rate, although both groups showed an improvement in certain aspects of sperm quality. The general conclusion was that glandular infections can regress spontaneously and that any resulting increase in sperm quality does not improve the chances of conception.

A systematic literature review done in France in 2017 that collated data relating to the effects of drugs treatments on male fertility showed that Nitrofurantoin caused decreased count and motility of spermatozoa in humans and that at high doses it might even lead to potential blockage of spermatogenesis by preventing the uptake of the carbohydrates and oxygen that are required for the correct function of cells involved in spermatogenesis. In the same review, cotrimoxazole (trimethoprim/sulphamethoxazole) was shown to cause decreased sperm motility, though in vitro.

Macrolides (erythromycin) and aminoglycosides (gentamicin) were noted to cause a decrease in sperm motility and survival of spermatozoa, and decrease in sperm parameters in rats respectively while penicillins and quinolones (ofloxacin and ciprofloxacin) cause moderate decrease in sperm parameters in animals. There is no reported effect on humans yet. This effects on sperm parameters (decrease sperm count and motility), are reversible after stopping the antibiotic treatment. However, despite these notable undesirable side effects of these antibiotics, it is recommended that once there are testicular infections and epididymitis, antibiotic treatment is recommended as a result of its favourable impact on sperm quality.

Anti-Inflammatory agents used in the treatment of Reproductive Tract Infection and their association with Male Infertility

Reproductive tract infection and inflammation are recognised as critical causative factors of male infertility. Inflammation of the reproductive tract may cause a rise in the seminal fluid leukocytes resulting in undue production of reactive oxygen species (ROS). ROS play a vital role in the cellular defence mechanism against inflammation; however, this may destroy spermatozoa at the same time. Inflammation can also impair fertility by increasing sperm agglutination, reducing sperm motility, obstructing the ejaculatory ducts and may result in a disturbance in epididymal sperm maturation affecting both motility and fertilizing ability of the spermatozoa.

Anti-inflammatory agents, in combination with antibiotics, are useful in treating male reproductive tract infections; however, they may have some effect on male fertility. The microorganism causing reproductive tract infection can be microbial or inflammatory forms. The inflammatory types cause leukocytospermia (seminal fluid leukocyte concentration >10^9/mL) and/or overproduction of ROS. This increased number of leukocytes sometimes persists even after treatment with only antibiotics for microbial forms especially in patients with complicated infection of the male accessory gland like prostate vesiculo epididymitis (PVE). In addition to leukocytospermia, there is abnormal sperm concentration, motility and morphology as well as other signs of inflammation in such patients. These patients, therefore, may benefit from steroidal and non-steroidal anti-inflammatory drugs (NSAIDS) that can be administered pre or post antibiotic administration.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Selective Cyclooxygenase-2 (COX-2) inhibitors

Several NSAIDS like COX-2 selective Nimesulide with a good analgesic activity and a unique action of ‘scavenger’ of superoxide anions from neutrophils have been tried in the past. A study conducted in Nigeria on the effects of nimesulide on testicular functions in prepubertal albino rats male albino rats concluded that at regular doses nimesulide may not be spermatoxic, but there is a concern that at higher doses, it may have toxic to the testis in albino rats.

Another study conducted in Italy on 30 cases of prostato-vesiculitis who had no fertility issue showed that following the administration of nimesulide orally at the dose of 100mg twice/day for three cycles of 10days there were evidence of improved inflammatory signs after transrectal prostate ultrasound evaluation and also marked reduction in the number of abnormal forms of sperm, however there was no statistically significant changes on sperm count and motility. Patients undergoing assisted reproductive technique, treated with rofecoxib (a COX-2 inhibitor), have shown improved sperm motility and morphology and decreased seminal fluid leucocyte concentration. Another study where patients were administered valdecoxib showed similar result.

However, this therapeutic approach to treat infertile patients with leukocytospermia needs further research.

Profens: Some data available on profens shows that ibuprofen may cause substantial alteration of sperm parameters and chromatin/DNA integrity in mice. These harmful effects are dose-dependent and are noticed in the early and late stages of drug administration. Another clinical trial with young men exposed to ibuprofen revealed that ibuprofen causes ‘compensated hypogonadism’ a condition common among elderly men and associated with physical and reproductive disorders, testosterone / luteinizing hormone ratio also reduced. It was demonstrated that that ibuprofen disrupts the endocrine system through selective transcriptional repression in the human testis leading to compensated hypogonadism.

Oxicams: There is a lack of information, on the association of Oxicams with infertility in men. It is generally advised that NSAIDS should be entertained for the treatment of acute forms of accessory gland inflammation to relieve symptoms and...
should be discouraged for chronic usage as much as possible in patients with history of infertility.7

Salicylates: Salicylates have been associated with decrease in sperm motility. The study by Porat-Soldin showed that there was marked decrease in sperm motility following administration of 650 mg of salicylate four times a day for 72 hours to four healthy males.126 There is no available data on salsalate and diflunisal.

Steroidal Anti-inflammatory Drugs: Steroidal Anti-inflammatory drugs like prednisolone may be employed in the treatment of accessory gland inflammatory alterations. A study that evaluated the effect of glucocorticoids on sperm parameters following treatment of patients presenting with accessory gland inflammation with glucocorticoids revealed that there is an association of steroids with fertility. It showed that prednisone treatment could significantly improve sperm parameters in a selected population of oligozoospermic patients with accessory gland inflammation. Glucocorticoids have also been shown to be beneficial in treating of infertility when antisperm antibodies (ASA) are implicated. Though the mechanism of ASA causing male infertility has not been conclusively elucidated. A recent meta-analysis has revealed a notable effect of ASA on sperm motility and concentration.127

CONCLUSION

The etiopathogenetic process(s) should be determined for clinicians to choose the best therapy to resolve male infertility. Antibiotics, anti-inflammatory medications, antioxidant and micronutrients are among the common medical repertoire. Antibiotics are suggested if there any identified urogenital infection. Tetracyclines, macrolides, trimethoprim and antibiotics B-lactam (penicillin derivatives, cephalosporins, monobactams and carbenapens) are the antibiotics most commonly prescribed. Leucocytospermia and/or inflammatory signs and/or symptoms should be treated with anti-inflammatory medications. Micronutrients and antioxidants find high relevance in protection of spermatozoa from oxidative stress in various pathological conditions. It covers a wide range of molecules which can be administered alone or combined. To conclude, several non-hormonal compounds are available for treatment of male infertility which allows for a customized clinical approach.

Conflict of Interest

The authors declare no conflict of interests

REFERENCES AND NOTES


80. A. Ilfergane, R. Henkel. Effect of Typha capensis (Rohrb.) NE Br. rhizome extract F1 fraction on cell viability, apoptosis induction and testosterone production in TM 3-Leydig cells. *Andrologia* 2018, 50(2), e12854.


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