Significance of Positive Semen Culture and Role of Antibiotics in Management of Oligo Astheno Terato Spermia (OATS)

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ABSTRACT
Infections of the genital tract are considered common causes of male fertility disorders, with a prevalence of 6–10%. Most of the affected men are asymptomatic, and the semen reports during the evaluation of infertility only are suggestive of pyospermia or the sperm cultures done are positive for microorganisms. Inconsistent diagnostic criteria have been applied to date, and this may explain the controversial debate about the role of infection and inflammation in the genital tract as a cause of oligoasthenozoospermia (OAT) leading to male infertility. This review is based on pertinent publications retrieved by a selective literature search in PubMed, including guidelines from European Association of Urology (EAU), AUA and systematic review articles, and attempts to identify and establish a cause and effect relationship between a seminal infection and OAT, if any exists.

INTRODUCTION
Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is solely responsible in about 20% of infertile couples and contributory in another 30-40%.1 Idiopathic infertility and Varicocele account for majority of cases. The presence of pyospermia and the countless semen cultures performed on infertile men, with widespread prescription of antibiotics, has created the controversy regarding the validity of such antibiotic use.

Can urogenital infections influence male fertility potential? The answer has long been a matter for debate with some authors convinced that it does, whilst others do not.2

Although unproven, yet urogenital infections can influence male infertility either directly by affecting the sperm, or indirectly, resulting in either obstruction or non-destructive lesions of the male excretory ducts, or, finally, in the production of anti-sperm antibodies affecting sperms. The cause-effect relationship between bacterial infections and semen contamination and male infertility is still being debated. To complicate the problem even more, the presence of bacteria in semen samples of infertile men has a similar prevalence to that observed in fertile males.3 The clinical significance of bacteria in semen is still unclear. It is also important to differentiate pyospermia from other causes of round cells in a semen sample and hence important to discuss this with the pathologist to confirm pyospermia.

DISCUSSION
What is Oligoasthenoteratospermia (OATS)
Oligoasthenoteratospermia (OATS), a reduction in motility and number of spermatozoa and a change in their morphology, is one of the most relevant causes of infertility in men.2
Once the repeated semen analysis done with all due precautions is suggestive of oligoasthenoteratospermia, the andrologist performs some investigations to identify the causes, and see if there is any possible treatment. Unfortunately, a clear cause of OAT with a specific treatment can only be found in 10-20% of the cases. As seen frequently in clinical practice, the cause is often not identified (idiopathic oligoasthenoteratospermia), or if identified, there is no definitive treatment. The effects of urogenital infection as a definitive cause of OAT and male infertility are controversial.3,4

Pus cells in semen: Significance?
The number of seminal fluid leukocytes may increase secondary to infections and/or inflammation of the urogenital tract, and their activation results in a ROS overproduction. In fact, leukocytes, under physiological conditions, may produce up to 1000 times more ROS than spermatozoa.3 This production of ROS plays an important role in the cellular defence mechanism against infections and inflammation but at the same time may damage spermatozoa. An increased number of leukocytes in the seminal plasma can also be present in varicocele, long sexual abstinence, or exposure to environmental factors.6-11

In contrast to the general view that leukocytes have a detrimental impact on sperm, a recent review cited a few reports indicating no detrimental effect of leukocytes on sperm.12-14 Some recent reports even attribute significant positive effects to seminal leukocytes.15-17 Despite uncertainty regarding the levels of leukocyte contamination that are critical, it is argued that a certain elevated number of leukocytes is beneficial to sperm concentration, motility and acrosome reaction because leukocytes might eliminate defective spermatozoa by phagocytosis and may even stimulate sperm functions through the release of ROS.12

Role of bacterial infection in causing OATS
Presence of leukocytes in the semen sample may not be an indication of underlying bacterial infection, especially in absence of clinical symptoms. Leukocytes are present in the genital tract of both male and female, even in healthy, fertile individuals not having an infection.18 In the light of the potential contamination of ejaculate samples with urethral commensals, bacteriospermia does not necessarily indicate genital infection.19,20 For uropathogenic bacteria, a threshold of 10³ colony-forming units (CFU)/mL has been suggested to define “significant” bacteriospermia.21 In cases of male genital tract infections and inflammations, however, fertility including sperm functions22,23 is seriously affected as clinical findings show oligozoospermia, asthenozoospermia or even azoospermia.24,25 These quantitative and qualitative changes can be triggered in various ways, namely, direct action of the pathogens on spermatozoa via agglutination26 or indirectly by inducing inflammatory processes in the seminal tract by activating leukocytes.27 In a large study comprising of more than 4000 patients consulting for infertility, the prevalence of male genital tract infection-related infertility varied between 10 and 20% and amounted to up to 35% in non-selected cases.28 In a recent research study from Tamilnadu, India, to determine the seminal patterns and prevalence of bacteriospermia and their impact on semen quality among infertile men, authors concluded that the presence of asymptomatic bacteriospermia did not correlate with abnormal semen parameters.29

Significance of Positive Semen Culture Report in Management of OATS
True bacteriospermia may be associated with causation of infertility and studies have indicated that antibiotic treatment of positive semen cultures increases pregnancy rates for in vitro fertilization.30-33 Others have reported lower fertilization rates with semen containing pathogenic organisms but not with semen containing only contaminants or commensals.34 In clinical practice, usually no precautions are taken to minimize the risk of contaminants in semen cultures. Generally uncounseled about how to collect semen for laboratory analysis, men routinely give semen specimens without cleaning the hands and genital areas with an antimicrobial wash. Thereafter, men with positive semen cultures are essentially treated with antibiotics before an in vitro fertilization cycle without making the distinction between true infection and contamination of the specimen. As a result, positive semen cultures that may have contaminants are unnecessarily treated with antibiotics. Also, there are limits to the usefulness of prewashing, since commensal organisms that colonize the anterior urethra are unaffected by it.35 Fortunately these organisms have no effect on fertility.34
Study by Francis y. Kim et al suggest that most positive semen cultures are the result of contaminants in asymptomatic infertile men. A significant reduction in enteric contaminants can be achieved with an effective antibacterial skin preparation, which would otherwise have been erroneously treated. Authors were able to isolate true pathogens with greater specificity with than without an antibacterial skin preparation. An antibacterial skin preparation reduces false-positive cultures by at least 50%, which would lead to a significant reduction in treatment costs and morbidity.

**Sperm Antibodies Testing**

Testing for sperm antibodies in search of cause for OATs is controversial. Not uncommonly, False positive results occur and treatment is advised based on reports; Improvement in OATs is not certain as antibodies do not necessarily impair sperm function. Antibodies may be found in genital infections and obstructions, but specific treatment is of limited value. Corticosteroids have been used successfully for high titre sperm antibodies. However, severe side effects may occur, including bilateral necrosis of the hip and gastric ulceration. In such cases of unproven certainty and higher risk of side effects, In-vitro fertilisation is a more effective and safer way to achieve pregnancy.

**Use of Antibiotics and Sperm Toxicity**

Although the antibiotic treatment has been widely advocated to preserve or restore normal sperm parameters in urogenital infections, some of these commonly prescribed antibiotics are found to have spermotoxic effects and affect fertility adversely. Although this side effect has not yet been directly shown in humans by randomized clinical trials, there are data concerning testicular and/or sperm toxicity for some antibiotics in rats or mice. These include ciprofloxacin and pefloxacin, ofloxacin, lomefloxacin, tetracyclines, cefonicid and other cephalosporins, and norfloxacin in quails. Schlegel PN et al in a review article warned that treatment with antibiotics may adversely affect the fertility potential of men and urged for the need of further investigation into the relative toxicity of antibiotics and the mechanisms by which antibiotics affect spermatogenesis and spermatozoal function.

**Financial and Psychosocial Burden Of Prolonged Empirical Medical Management on the Subfertile Male and Couple**

Despite infertility being classified as a disease and males contributing to almost half of all infertility cases, coverage for male infertility management is often excluded from health insurance laws. Antibiotics and antioxidants are frequently prescribed empirically for an extended duration in anticipation to cure seminal bacteraemia and subsequently improve the seminal parameters of previous OATs which often impacts heavily on patient’s financial status and ability to pursue the overall fertility management as a couple. The uncertainty of any proven benefit over OATs with empirical medical and antibacterial management also has negative psychological implications over the couple undergoing treatment for infertility.

**Guidelines Recommendations:**

1. **European Association of Urology (EAU):** Conclusions and recommendations for male accessory gland infections

   **Conclusions:**
   a. Urethritis and prostatitis are not clearly associated with male infertility.
   b. Antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction.
   c. Although antibiotic treatment for Male Accessory Gland Infections (MAGI) might provide improvement in sperm quality, it does not necessarily enhance the probability of conception.

   **Recommendation:** Patients with epididymitis that is known or suspected to be caused by N. Gonorrhoeae or C. Trachomatis must be instructed to refer their sexual partners for evaluation and treatment.


   An elevated number of white blood cells in the semen has been associated with deficiencies in sperm function and motility. Under wet mount microscopy, both leukocytes and immature germ cells appear similar and are properly termed "round cells." Many laboratories improperly report all round cells as "white
blood cells." The clinician must make sure that the two types of cells are differentiated. A variety of assays are available to differentiate leukocytes from immature germ cells. These include traditional cytologic staining and immunohistochemical techniques. Those patients with true pyospermia (greater than 1 million leukocytes per ml) should be evaluated for a genital tract infection or inflammation.

**Recommendation:** Specialised tests on semen are not required for diagnosis of male infertility. They may be useful in a small number of patients for identifying a male factor contributing to unexplained infertility, or for selecting therapy, such as assisted reproductive technology.

**CONCLUSION**

The cause-effect relationship between bacterial infections/semen contamination and male infertility is still being debated. Inconsistent diagnostic criteria have been applied to date, and this may explain the ongoing controversial debate about the role of infection and inflammation in the genital tract as a cause of OAT leading to male infertility. In general, routine semen cultures should not be obtained and desired only in subfertile men with symptoms or persistent WBCs in semen. Only these cases should be prescribed with culture specific antibiotics. Persistent pyospermia or positive cultures should not be obtained and desired only in leading to male infertility. In general, routine semen and inflammation in the genital tract as a cause of OAT have been applied to date, and this may explain the on-going controversy about the role of infection and inflammation in male infertility. Central European Journal of Urology. 2013;66(1):60–67.


http://www.uroweb.org/guidelines/online-guidelines/ male infertility

http://www.auanet.org/guidelines/male-infertility-optimal-evaluation