



Neisseria Gonorrhoeae: A Cause of Male Infertility

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Abstract

Background: Gonorrhoea is a sexually transmitted infection that is commonly related to male infertility. The infection affects sperm transport through the urinary tract and subsequent damage of the testicular tubes. The infection also impairs sperm production as the infection is rarely asymptomatic and can be difficult to diagnose, it is possible that its contribution to male infertility is underestimated. Infection of the genitals results in a purulent (pus-like) discharge from the genitals which may be foul smelling, inflammation, redness, swelling, dysuria, and a burning sensation during urination. As with Chlamydia, it is possible to have a Gonorrhoea infection without noticeable symptoms, and which can cause permanent scarring and blockage in the sperm production duct. Gonorrhoea is a bacterial infection and is treatable with antibiotics. Laboratory studies reveal that *N. gonorrhoeae* infection can impair motility, viability and spermatogenesis; increase anti-sperm antibodies are associated with a decrease in semen parameters as a result of the production of anti-sperm antibodies in the genital tract.

Aim: The study aimed at reviewing the possible role of gonorrhoea in male infertility.

Method: Research publications such as Pubmed, Scopus, Medline etc.

Results: over 115 journals of international repute were obtained, out of which 50 were found to be closely relevant such as; the implication of *N. gonorrhoeae* in male infertility, complication of *N. gonorrhoea* infection, *N. gonorrhoeae* and male infertility and were reviewed.

Conclusion: *N. gonorrhoeae* was found implicative in male infertility and the need for comprehensive modern laboratory methods for the diagnosis of the infection and also to include routine laboratory tests.

Keywords: *N. Gonorrhoea*; Male Infertility; Urethritis; Epididymitis; Epididymal-Orchitis

Abbreviations: WW1: World War One; HIV: Human Immunodeficiency Virus; STI: Sexually Transmitted Infection; PMN: Polymorph Nuclear Leukocyte; TNF: Tumour Necrosis Factor; LPS: Lipopolysaccharide; PID: Pelvic Inflammatory Disease; OA: Obstructive Azoospermia; IF: Immunofluorescent; CF: Complement Fixation; DFA: Direct Fluorescent Antibody Stain; EIA: Enzyme Immunoassays; Naats: Nucleic Acid Amplification Tests; PCR: Polymerase Chain Reaction.

Introduction

Background History

Antediluvians Egyptian, Chinese, Greek along with Roman literature as well as the Bible, all described symptoms related to gonorrhoea [1] and the term gonorrhoea is rooted from ancient Greek and was first used by Galen in 130 A.D, meaning the flow of seed. Albert Neisser was the first

to identify the aetiological agent of gonorrhoea in 1879 in microscopy of stained smears from vaginal, urethral and conjunctival exudates [2] and termed it *Micrococcus gonorrhoeae*. Many other terms have historically been used for *Neisseria gonorrhoeae*; [3,4]. Previous to the discovery of operational antimicrobial therapy of *N. gonorrhoea*, urethral irrigation, asceticism from alcohol and sexual activity, rest and systemic treatment with a range of balsams were the conventional therapy regimens [5]. Throughout World War One (WW1), prophylactic packets were given to soldiers, containing condoms, calomel cream and Argyrol [6]. After the successful culturing of *N. gonorrhoeae* by Leistikow in 1882 duo with the discovery of Gram's staining by Gram in 1884, and carbohydrate oxidation test by Elser and Huntoon in 1909, diagnosis of gonorrhoea improved significantly. The discovery of sulphonamides for the management of gonorrhoea soon after penicillin, the prospect of eradicating gonorrhoea was high, resulting in the rapid decline of gonorrhoea occurrence [6-8]. It was soon discovered that *N. gonorrhoea* has a remarkable capability to adapt to and outlive any antimicrobial therapy, and continues as a key sexually transmitted infection (STI) [9]. In the early 1960s, this trend reversed with the inception of oral contraceptive methods, and *N. gonorrhoea* infections reached a climax incidence of over one million reported cases in 1978 in the United States [9]. In the late 1980s, with the outbreak of the Human Immunodeficiency Virus (HIV) and concurrent prevalent use of barrier contraceptives, the incidence of gonococcal infection again declined [10]. The contemporary upsurge in all sexually transmitted diseases is presently observed globally, as a result of the emergence of antibiotic resistance amid organisms causing these diseases [11].

Sexual contact vaginally, anally or orally with an infected person serves as the basic mode of *N. gonorrhoeae* transmission; conversely, pregnant women with the gonococcal disease can transmit this bacterium to their offspring during birth [12,13]. Successful colonization by the gonococcus results in a broad spectrum of clinical manifestations of the disease that are, in part, determined by the particular strain that initiates the diseased state and the anatomical site of infection.

Currently, *N. gonorrhoeae* is highly sensitive to zoliflodacin and gepotidacin which are newly developed antibiotics. Nonetheless, the gonococcus easily develops resistance to antimicrobials, so how long these antimicrobials will remain potent is only time can reveal [14]. There is an alarming increase resistant of *N. gonorrhoea* to many antibiotics and conversely increase in male infertility globally [15]. Therefore, the goal of this appraisal is to present contemporary information on Neisserial infection as one of the causes of male infertility. Pub Med, Medline and Science Direct databases were used as the search engine for

published articles related to *N. gonorrhoeae* as a cause of male fertility.

Gonococcal Pathogenesis

N. gonorrhoeae is closely related to *N. meningitides* and typically colonizes the mucosal epithelia of the male urethra and the female uterine cervix, but infections can also occur on the rectum, the throat and the conjunctiva of the eye. The latter can easily happen to newborns if the mother carries the pathogen, *N. gonorrhoeae* transmission generally occurs through direct vaginal, anal and oral sexual contact, but indirect modes of transmission have been reported leading to establishment of urogenital tracts infection through interaction with non-ciliated epithelial cells resulting in cellular inversion [16]. Attachment to the mucosal epithelium is followed within 24-48 hours by penetration of the organism between and through epithelial cells to the sub mucosal tissues. This is followed by massive infiltration of the infected epithelial tissue by neutrophils, resulting in the development of sub mucosal micro abscesses and exudation of pus [17].

Although different molecular mechanisms are involved during the establishment of gonococci on the mucosal surfaces of males and females, infection often leads to inflammation and polymorph nuclear leukocyte (PMN) influx. Both tumour necrosis factor (TNF) from phagocytes and gonococcal products, such as peptidoglycan and lipopolysaccharide (LPS), also cause toxic damage to ciliated epithelial cells of mucosal surfaces [18].

Epidemiology

Averagely, 62 million new cases of gonorrhoea are been reported annually worldwide with the greatest number of cases occurring in South and Southeast Asia and Sub-Saharan Africa [19]. However, the occurrence of new cases is still prevalent among construction workers globally and in heavily industrialized regions including Eastern and Central Europe, North America, and Western Europe [19]. Gonorrhea rates declined globally in the 1940s and 1950s with the advent of penicillin therapy [20], but began to rise again between 1966 and 1975 as a result of the changing sexual behavior patterns among people and increasing resistance to penicillin G [19,21]. In response to this, public health officials and health care providers launched a national campaign to control the spread of gonorrhoea through the widespread screening of asymptomatic women using newly developed selective culture media (Thayer-Martin). This approach and the increasing use of condoms were largely successful, yielding a decline in the number of diagnosed gonorrhoea cases [19,21]. Nonetheless, the number of cases of gonorrhoea increases again between 2005 and

2007 globally, with the overall current rate of gonorrhoea transmission remains high.

West Africa has recorded a low prevalence of both *Chlamydia trachomatis* and *N. gonorrhoeae* when compared with East Africa and the Western world [22,23]. Women presenting with vaginal discharge in six countries in West Africa (Benin, Burkina Faso, Ghana, Guinea, Uganda, and Mali), tested a 3.2% prevalence [24]. A recent study conducted by Yirenya-Tawiah and others to investigate the prevalence of *C. trachomatis* and *N. gonorrhoeae* in women of reproductive age living in urogenital schistosomiasis endemic areas in Ghana showed 6.3% and 2.6% positivity of Chlamydia and Gonorrhoea respectively. Samples were examined using PCR incorporating the use of Cobas Amplicor from Roche Diagnostics. They concluded that women with a history of urogenital schistosomiasis were at a higher risk of contracting the diseases [25]. Many studies have shown that infections of the reproductive tract both in men and women may impair reproductive function. However, some studies also showed the Prevalence rate of *N. gonorrhoeae* infection amongst undergraduate female students in the University of Port Harcourt between January and June 2009 was 5% [26]. This result is comparable to those of Franceschi and Gopal et al. who had 2.6% and 3.8% respectively.

Risk Factors

Neisseria gonorrhoeae (gonococcus) is the etiologic agent of gonorrhoea [27]. Gonorrhoea, the infection caused by the gonococcus, is the second most commonly reported notifiable disease in the United States today (CDC, 2007). Studies indicate that the mechanisms of infection differ in men and women [7,28]. Therefore, younger age, new sex partner, sex partner who has concurrent partners, multiple sex partners, previous history of gonorrhoea infection and having other sexually transmitted infections are some of the most common risk factors of contracting gonorrhoea infection, others include immune compromised individual, prostitution, illicit drug abuse, low socioeconomic status, early onset of sexual activity, unmarried status and genetic factors [29-32].

Impact on Male Reproduction

The term gonorrhoea, meaning "flow of semen," was first termed by Galen in 130 AD, who presumed that the urethral exudate of infected males was semen [27]. The impact on fertility has been well established. In fact, in women, *N. gonorrhoeae* infection may cause pelvic inflammatory disease (PID) and lead to chronic pelvic pain, ectopic pregnancy, and infertility. CDC, 2009 [33]. *N. gonorrhoeae* is also known to be involved in damage to the female reproductive tract and has been recognized as a cause of PID, together with

Gardnerella vaginalis and *Trichomonas vaginalis* [34,35]. Some studies showed that *N. gonorrhoeae*, other bacteria, yeasts, and protozoa may interact directly with sperm. These interactions result in attachment between bacteria and sperm, agglutination phenomena and morphological alterations to sperm [36]. Furthermore, the presence of pathogenic bacteria in the vagina has been associated with the release of pro-inflammatory cytokines, and a correlation between elevated IL-beta and IL-8 and idiopathic fertility was demonstrated [34].

Men who become infected with *N. gonorrhoeae* usually present with acute anterior urethritis, prostatitis, epididymitis, proctitis, reactive arthritis, and decreased fertility which is accompanied by symptoms of urethral discharge and dysuria [27,7]. Urethritis is the inflammation of the urethra (urine tube) that runs along the underside of the penis. Symptoms include a white cloudy discharge from the tip of the penis, pain or a burning sensation when the patient urinates; urge to urinate often, irritation and soreness around the tip of the penis. Although there are many causes of urethritis *N. gonorrhoeae* infection is the most common [37]. The incubation period in males is between 2-8 days, but can equally take up to 10 days or even longer [7,15,27,38]. However, approximately 1 per cent of men can be asymptomatic for up to 6 weeks after exposure [27]. This has been linked to infection by particular *N. gonorrhoeae* strains, namely arginine, hypoxanthine, and uracil auxotrophs referred to as AHU- strains [39].

Prostatitis is one of the most common urological disorders and can affect men of any age. Approximately one-third of all men during their lifetime will experience symptoms consistent with prostatitis [37]. The early classification of prostatitis described four syndromes for which pelvic pain in the male was the common factor. The NIH classification system designates categories I and II for cases in which bacteria cause acute or chronic prostatitis, respectively. In acute bacterial prostatitis, patients can present with voiding complaints, such as dysuria, frequency, urgency, or hesitancy. Other symptoms can include suprapubic pain, hematuria, or systemic symptoms such as fever, chills, nausea, vomiting, or malaise [37,40].

Epididymitis is a condition that causes swelling and tenderness in the epididymis. The epididymis is part of a man's reproductive system that carries sperms from the testicles, so if the testicles are affected, it is called epidymo-orchitis. Gonorrhoea may cause painful testicles or infertility by blockage of epididymis or tubes, then the spermatozoa are unable to move out of the genitourinary tract causing a condition known as obstructive azoospermia (OA) which by implication means there are no spermatozoa in the ejaculated semen leading to sterility of the semen fluid [41].

Gonorrhoea infections that go undetected and untreated in men for a long time, lead to epididymitis - affecting the ducts that are attached to the testicles where spermatozoa mature. Epididymitis can cause the infected testicle to shrink, abscesses, and sores in the surrounding scrotum area, the structures of the male reproductive tract, including the epididymis and urethra, can equally be damaged by infection with untreated gonorrhoea. Although uncommon among men but has a serious impact on male infertility. Therefore, Gonorrhoea complication in men can optimally cause infertility [42].

Laboratory Diagnosis

Laboratory diagnosis of *N. gonorrhoeae* has traditionally consisted of direct microscopy of Gram- or methylene blue stained smears of urethral specimens from men or women and culture of fastidious *N. gonorrhoeae* prepared from urogenital specimens and currently, the antigen and nucleic acid detection technologies are developed [40,43,44]. Antibodies to Neisseria spp. are detected with immunofluorescent (IF) assay, but these assays are expensive, low sensitivity and not widely available. The IF and complement fixation (CF) tests are not too sensitive in the diagnosis of urogenital infection. The value of Neisseria-specific antibodies (IgM, IgG, IgA) in the diagnosis of urogenital infections using indirect immunofluorescence (IF) method is limited since these antibodies are not genus-specific and thus will also be elevated in infections with non-pathogenic Neisseria strains. Concerning high specificity, the bacteriological culture has been the method of choice for diagnosis. Another advantage is that these cultures maintain the viability of the microorganisms for additional studies such as genotyping or antimicrobial susceptibility tests [21,44,45]. One disadvantage of culture is the low sensitivity of 70-85%. Furthermore, the costs, the high level of technical expertise necessary and the time required to obtain results, are significant disadvantages of this method. Rapid methods for diagnosis of an *N. gonorrhoeae* infection include a direct fluorescent antibody stain (DFA) and enzyme immunoassays (EIA) to detect antigens of the bacterium. Both types of assay have low sensitivities compared to culture and DNA amplification methods [21]. Compared to culture, the sensitivity of these assays, depending on many variables including the population examined and the culture technique used for comparison has been reported to vary from 50 to 90%. Because of their high sensitivity and specificity, and their possible use for a large range of sample types, nucleic acid amplification tests (NAATs) are the tests of choice for the diagnosis of *N. gonorrhoeae* genital infections. Several commercial NAATs are available and make use of different technologies: polymerase chain reaction (PCR) and real-time PCR, strand displacement amplification, transcription-mediated amplification, and nucleic acid sequence-based

amplification [46]. The major targets for amplification-based tests are generally multiple-copy genes, e.g. those carried by the cryptic plasmid of *N. gonorrhoeae*, or gene products such as rRNAs [15,42,47].

Treatment for Gonorrhoea

Many antibiotics can successfully cure gonorrhoea in adolescents and adults. However, drug-resistant strains of gonorrhoea are on the increase in many parts of the world, including the United States, West Africa, and Asia, successful treatment of gonorrhoea is becoming more difficult, because many people with gonorrhoea also have Chlamydia (another STI), antibiotics for both infections are usually given together [21,47,48]. Zoliflodacin and gepotidacin are new antibiotics currently effective for the treatment of *N. gonorrhoeae* infection [14].

Prevention of Neisseria Gonorrhoea Infection

The best way to avoid transmission of STIs is public health education, totally abstain from sexual intercourse before marriage and those who are married to remain faithful to their partners, or to be in a long-term mutually monogamous relationship with a partner who has been tested and is known to be uninfected [47]. Latex condoms, when used consistently and correctly, can reduce the risk of transmission of gonorrhoea, also the person and all of his or her sex partners must avoid sex until they have completed their treatment for gonorrhoea [48-50]. All persons at high risk of gonorrhoea infection must be screened for Chlamydia, HIV, and syphilis, above all, personal hygiene.

Conclusion

Infection with *N. gonorrhoeae* accounts for the rarely most common sexually transmitted infection globally. In men, *N. gonorrhoeae* can cause urethritis, epididymitis, epididymal-orchitis and prostatitis, although asymptomatic infections are often common. Acute and chronic infection and/or inflammation can cause partial or complete obstruction of sperm transport leading to oligozoospermia or azoospermia respectively. Subclinical gonorrhoea infection may activate an immune response to sperm. The infection of the testis and prostate is implicated in the deterioration of sperm, possibly affecting male fertility. Also, there is increasing evidence that the function of human spermatozoa can be significantly affected by direct exposure to the bacterium or by the host immune response induced by it. The role of leukocytospermia in the pathogenesis of male infertility remains unknown. The roles in which leukocytes and *N. gonorrhoeae* may result in sperm damage involve ROS generation and the induction of sperm apoptosis. On the other hand, the co-infection with *N. gonorrhoeae* and other microorganisms may be a cause

of the impairment of sperm quality, motility, and function. Efforts should be made at achieving proper diagnosis using a more sensitive method (NAAT), and adequate treatment is given promptly to avoid resistance and complications.

Recommendations

Screening for gonorrhea infection should be made mandatory for all intending couples and intermittently for all adults with multiple sexual partners. Modern laboratory diagnostic equipment should be made available in all STI clinics across the globe especially in developing countries. Public awareness should be taken seriously just like that of HIV/AIDS and those found with the infection should be promptly treated.

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