Chapter 5
Sexually Transmitted Infections

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Introduction

Sexually transmitted infections (STIs) have a high prevalence worldwide. STIs and their complications are one of the top five reasons to attend healthcare in the developing world [1]. In 2008, the US incidence rate of new STI infections was 20 million with a prevalence of 110 million. In 2010, the medical costs in the USA were $16 billion [2]. The effect of untreated STIs on pregnancy is well documented, as is the association with pelvic inflammatory and female tubal infertility. The effect of STIs and male accessory gland infection on male fertility is less clear. The evidence to date is conflicting as to the extent of impact. Most STIs are easily treated, and those that are at present incurable such as HIV can be treated and controlled to allow couples to conceive without harm to each other or the child. Another consideration when assessing a couple for fertility issues is male sexual function. Erectile dysfunction can prohibit penetrative sex. The psychological impact of a diagnosis of a STI, whether current or in the past, may well cause psychological issues that if addressed may improve sexual function, and thus the ability to conceive. For quick reference for testing and US recommended treatment of specific STIs, please refer to Table 5.1 and 5.2, respectively.

HIV

In 2010, an estimated 34 million people were living with HIV infection [3]. The global epidemic seems to have stabilized with a drop in incidence. In 2010, there were an estimated 2.7 million new infections compared to the peak of 3.2 million in

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J.P. Mulhall and W. Hsiao (eds.), *Men's Sexual Health and Fertility*,
DOI 10.1007/978-1-4939-0425-9_5,

Table 5.1 Tests available for sexually transmitted infections, site specific

Chlamydial infection	
Endocervical swab	NAATs
Urethral swab	Cell culture
	Direct immunofluorescence
	EIA
	Nucleic acid hybridization tests
Urine	NAATs
Vaginal Swab	NAATs
Rectal swab	NAATs
Oropharyngeal swab	Nucleic acid hybridization tests
Gonococcal infections	
Male urethral swab	Gram stain
	Culture
	Nucleic acid hybridization tests
	NAATs
Endocervical swab	Culture
	NAATs
Vaginal swab	NAATs
Urine	NAATs
Oropharyngeal swab	NAATs (not FDA approved)
Rectal swab	
Conjunctival swab	
Herpes Simplex Virus	
Direct swab	Viral culture
	Viral PCR
Serology	HSV-specific glycoprotein 1 and 2 Abs
HIV	
Serology First Line	HIV 1 and 2 EIA
Serology	Western Blot
Confirmation	Indirect Immunofluorescence
	HIV RNA assay
	p24 antigen
HPV	
Cervical swab	NAATs
Syphilis	
Direct test	Dark-field microscopy
	T. pallidum PCR
Serology	Syphilis EIA
	fluorescent treponemal antibody absorbed tests [FTA-ABS] tests, *T. pallidum* passive particle agglutination [TP-PA] assay, with either
	Venereal Disease Research Laboratory (VDRL)
	RPR
Trichomoniasis	
Vaginal swab	Wet prep microscopy

(continued)

Table 5.1 (continued)

	Culture
	NAATs
	Point-of-care tests (nucleic acid probe test immunochromatographic capillary flow)
Urethral swab	Culture
Semen	NAATs
Urine	NAATs

Table 5.2 US recommended treatment for specific STIs

Chlamydial infections	
1st Line	Azithromycin 1 g orally in a single dose
	Doxycycline 100 mg orally twice a day for 7 days
Alternative	Erythromycin base 500 mg orally four times a day for 7 days
	Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
	Levofloxacin 500 mg orally daily for 7 days
	Ofloxacin 300 mg orally twice a day for 7 days
Gonococcal infections	
1st Line	Ceftriaxone 250 mg IM with Azithromycin 1 g stat or doxycycline 100 mg twice daily for 7 days
Herpes Simplex Virus	
Primary infection	Acyclovir 400 mg 3 times a day for 7–10 days
	Acyclovir 200 mg 5 times a day for 7–10 days
	Famciclovir 250 mg 3 times a day for 7–10 days
	Valacyclovir 1 g twice a day for 7–10 days
Recurrent infection	Acyclovir 400 mg orally 3 times a day for 5 days
	Acyclovir 800 mg orally twice a day for 5 days
	Famciclovir 125 mg orally twice a day for 5 days
	Famciclovir 1000 mg orally twice a day for 1 day
	Famciclovir 500 mg orally once then 250 mg twice daily for 2 days
	Valacyclovir 500 mg orally twice a day for 3 days
	Valacyclovir 1 g orally once a day for 5 days
Suppression	Acyclovir 400 mg orally twice a day
	Famciclovir 250 mg orally twice a day
	Valacyclovir 500 mg orally once a day
	Valacyclovir 1 g orally once a day
HIV-1[a]	
Treatment naive	Efavirenz/tenofovir disoproxil/emtricitabine
	Ritonavir-boosted atazanavir + tenofovir disoproxil/emtricitabine
	Ritonavir boosted darunavir + tenofovir disoproxil/emtricitabine
	Raltegravir + tenofovir disoproxil/emtricitabine
Virological resistance	Regimen tailored to resistance tests and previous treatment history
HPV	
Genital warts	Imiquimod 5 % cream
	Podophyllotoxin 0.15 %
	Cryotherapy

(continued)

Table 5.2 (continued)

	Excision
	Electrosurgery
	Laser surgery
Precancerous cells	Stage dependent
Syphilis	
Early syphilis	Benzathine penicillin G 2.4 million units IM in single dose
Early latent syphilis	Benzathine penicillin G 2.4 million units IM in single dose
Late latent syphilis	Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units each at 1-week intervals
Syphilis of unknown duration	Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units each at 1-week intervals
Tertiary syphilis	Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units each at 1-week intervals
Neurological syphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as three to four million units IV every 4 h or continuous infusion, for 10–14 days or Procaine penicillin 2.4 million units IM once daily for 10–14 days with Probenecid 500 mg orally four times a day for 10–14 days
Trichomoniasis	
1st Line	Metronidazole 2 g orally in a single dose or Tinidazole 2 g orally in a single dose
Alternative regimen	Metronidazole 500 mg twice daily for 7 days

CDC. Sexually Transmitted Diseases Guidelines, 2010. Morbidity and mortality weekly report December 2010. Vol 59. No. RR-12. http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf. Accessed 18 August 2013

[a]National Institutes of Health. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/aa_recommendations.pdf. Accessed 18 August 2013

1997. The prevalence of HIV infection in people aged 15–49 years has remained constant at 0.8 % worldwide, though worryingly in some areas such as central Asia and Eastern Europe the prevalence has doubled in 8 years [4]. With the increased availability of Highly Active Anti Retroviral Therapy (HAART), there are now more people living with HIV infection despite the reduction in incidence. There are two types of HIV virus, HIV-1 and HIV-2. HIV-2 is a much rarer virus, mainly confined to Western Africa. HIV-2 is less aggressive, with a lower rate of progression to AIDS and a lower transmission risk compared to HIV-1. Some Antiretrovirals (ARVs) are not effective against HIV-2. All subsequent discussion will be about HIV-1 unless specified.

HIV is a retrovirus, an RNA virus that infects and replicates in human CD4 T cells. It is a blood borne virus and is transmitted through blood, blood products, sexual fluids, and exposure to other bodily fluids such as amniotic fluid, spinal fluid, and breast milk. The common routes of transmission are via sexual intercourse, mother-to-child transmission and by sharing injecting equipment. Initial infection

with HIV is most commonly asymptomatic. Symptomatic seroconversion illness consists of flu-like symptoms, myalgia, rash, headaches, and fevers. Later in the disease process, with the subsequent fall in CD4 count, other symptoms develop including loss of weight and then more specific opportunistic diseases associated with HIV infection. AIDS (Acquired Immunodeficiency Syndrome) is a diagnosis made using the CDC classification (Centers for Disease Control and Prevention). The individual has to have detectable HIV antibody and either an abnormal CD4 cell count ($<$200 cells/mm^3 or $<$14 % of all functioning lymphocytes) or an AIDS defining illness.

HIV infection can be diagnosed via a blood or saliva test. A confirmatory test (Western blot) is used after a positive HIV screening test. The fourth generation ELISA (enzyme-linked immunosorbent assay) is recommended for use in the UK by BHIVA (British HIV Association). This test detects not only antibodies to HIV 1 and 2 but also the p24 antigen, and thus, it can detect HIV infection before the patient becomes antibody positive. Rapid point-of-care tests for HIV infection are available. These are highly sensitive though not specific for HIV infection. Confirmatory testing is required for all reactive results.

The treatment for HIV-1 infection is HAART, normally a combination of three drugs that belong to at least two different classes. Recommendations for starting HAART and the choice of combinations are provided by BHIVA, EACS (European Aids Clinical Society), and the CDC.

HIV Infection and Conception

HAART has dramatically improved the life expectancy of those living with HIV. This and other advances in HIV care have reduced morbidity and increased survival. HAART has also had a dramatic affect on mother to child transmission (MTCT). A study in the UK of over 2,000 women virologically suppressed on HAART found the MCTC rate was 0.1 % [5]. With this in mind, fertility and conceiving with HIV infection has now become an important issue. In serodiscordant couples, where condom use is used to prevent transmission, options for safe conception are vital.

If the female is HIV positive in the serodiscordant couple, self-insemination is an option. To obtain the semen the HIV negative male can either ejaculate into a container or have sex using a non-spermicidal condom. Self-insemination with semen, using a sterile 10 ml syringe, can then be performed by the couple after about 30 min once the ejaculate has liquefied. In serodiscordant couples where the male is HIV positive sperm washing is the safest way to conceive. It protects the female partner and child from HIV infection. The technique separates the sperm from the seminal fluid and non-germinal cells that potentially carry HIV. The process uses centrifugation and a swim-up method that has been proven to provide spermatozoa that are HIV-1 RNA and proviral DNA negative [6]. This sperm is then used to fertilize the woman during ovulation via intrauterine insemination

(IUI) or, if needed, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). A multicentered retrospective study of over 3,390 cycles of sperm washing has not shown seroconversion in either the female partner or the child [7].

In 2008 "The Swiss statement" published by the Swiss Federal Commission on AIDS Related Issues stated clearly that after reviewing the literature, an HIV-infected individual is sexually noninfectious provided the individual complies with antiretroviral therapy (ART), the viral load has been non-detectable for at least six months and there are no additional sexually transmitted diseases present [8]. An interim report from the HPTN 052 study of heterosexual couples was subsequently released and showed that earlier initiation of ART led to a 96 % reduction in HIV transmission to the HIV uninfected partner [9]. With this information, in situations where sperm washing is not an option, some couples may wish to try to conceive naturally. To limit the exposure of the HIV negative partner, BHIVA guidelines recommend discussion on the fertility cycle and timed conception. Additional screening for fertility should be offered before unprotected sex commences to ensure conception via natural methods is likely [10].

Pre-exposure chemoprophylaxis (PrEP) is the use of daily antiretroviral medication in HIV seronegative people to reduce the risk of becoming HIV seropositive through sexual exposure. The FDA has recently approved the combination of tenovofir and emtricitabine for use in PrEP. This would be an alternative option in serodiscordant couples. The "Partners in PrEP Study" led by the University of Washington's International Clinical Research Center showed a reduction in risk of HIV transmission by 75 % (95 % CI 55–87 % $p < 0.001$) using once daily tenofovir–emtricitabine (Truvada) [11].

HIV Infection and Fertility

HIV can affect fertility in a number of ways. There have been several studies showing abnormal semen parameters in HIV positive males. A relatively large study showed that ejaculate volume, sperm concentration, total count, progressive motility, and normal morphology were all significantly lower in HIV positive men. There was a significant positive correlation observed between CD4 count and sperm concentration, total count, motility, progressive motility, and post-preparation concentration and also a significant negative correlation with normal sperm morphology [12]. Interestingly, this same study showed that an HIV viral load of $<$1,000 copies/ml and receiving HAART significantly improved IUI outcome, indicating a secondary benefit from being on treatment. Other studies suggest HIV positive men have more viscous semen containing fewer motile sperm and more round cells [13]. It has been shown that with prolongation of survival in AIDS patients there was more pronounced loss of germ cells within the testes [14]. HIV infection is known to cause secondary hypogonadism and a thus a low testosterone level [15]. Low testosterone is associated with a reduction in sperm count. HIV positive men are more likely to suffer from erectile dysfunction and low sexual

desire [16]. Patients on HAART were found to have raised estradiol levels that were associated with low sexual desire [16, 17]. Low sexual desire and erectile dysfunction may impact further on the ability to conceive. With regard to HIV positive females, prior to antenatal screening and HAART there was a 67 % increased risk of spontaneous abortion. In the HAART era, HIV positive women are still less likely to conceive, but when they do they have miscarriage rates similar to HIV negative women. Despite some ARVs being associated with preterm labor there has been an overall reduction in stillbirths and prematurity. Though IVF is available for HIV positive women the pregnancy rates are lower than the normal population. There is ovarian resistance to hyperstimulation which is independently associated with CD4 count [18]. There is also a theoretical risk to the embryo of HIV transmission with invasive techniques used but more evidence is required.

Herpes Simplex Virus Type I and II

Genital herpes is caused by Herpes Simplex Virus (HSV) type 1 and 2, members of the Herpesviridae family. The virus has an active and latent phase. After the primary infection the virus is transported along the sensory nerves to the nerve bodies where it multiplies. The virus travels back along the nerve axon to the skin continuously, though reoccurrence occurs only when the virus is no longer controlled by the CD8 dermal cells [19]. The episodes of active disease tend to reduce in frequency and severity over time. Up to 90 % of people who are HSV type 2 antibody positive have never knowingly had an outbreak of genital herpes [20]. Transmission is most likely during periods of active disease but asymptomatic shedding of the virus does occur without evidence of lesions [21].

HSV infection presents initially as erythema, progressing to blisters on the skin. These break down to form painful ulcers, most commonly on the genitals or around the mouth. There may be a preceding prodromal phase of flu like illness, aching in the groin or tingling over the skin prior to lesions appearing. The primary infection is often the most severe. This can be associated with fever, headache, malaise, and myalgia, and can lead to complications such as urinary retention or aseptic meningitis. It is also associated with miscarriage in pregnancy.

Diagnosis was previously made by viral isolation and culture. With the development of PCR techniques the diagnosis of HSV has improved. Serum antibody tests can be performed but this only confirms previous exposure to HSV 1 or 2 and does not predict whether the patient has symptomatic disease. Treatment of a primary episode is with antiviral medication such as acyclovir. Supportive treatment such as analgesia and topical lidocaine may also be needed. With recurrent episodes treatment needs to be implemented early to have maximal impact on the duration of symptoms. In frequent or severe recurrence, suppression therapy may be indicated with daily antivirals.

HSV and Fertility

Conclusive evidence for the association of HSV 1 and 2 on fertility is lacking. HSV DNA has been found more frequently in infertile men [22]. Studies have shown HSV is associated with significantly lower sperm count and motility [23–25]. In HSV positive men reduced citrate and alpha glucosidase levels, associated with impaired prostate and epididymal function, have also been observed [24]. Treatment of both couples for HSV with acyclovir has lead to pregnancy in some small studies [26, 27]. Other studies have shown no effect of HSV on sperm parameters [22, 27, 28]. Genital HSV transmission is via skin to skin contact. Though condoms offer a degree of protection depending on the site of viral shedding HSV transmission may still occur. HSV is a very stigmatizing disease, in part due to the incurable nature of the virus. In August 2011, a man was jailed in the UK for transmitting HSV-2 to his partner as he did not disclose his status. The psychological distress and psychosexual problems associated with a diagnosis of HSV infection and recurrent HSV infections have been well described in the literature, though there is some debate as to whether these are due to long term effects of HSV infection or whether some patients are predisposed to anxiety [29–31]. In recurrent genital herpes suppressive treatment with daily antiviral therapy has been shown to improve quality of life, reduce anxiety [32] and reduce transmission rates [33]. The reduction in transmission rate is important for serodiscordant couples who wish to conceive but normally rely on condoms to prevent transmission.

Human Papillomavirus

Many types of Human Papillomavirus (HPV) have been isolated that affect the genital region and are transmitted via sexual contact. The most common types are HPV 16 and 18, high-grade oncogenic viruses, and HPV 6 and 11, low-grade viruses responsible for genital warts. The prevalence of HPV infection in the USA has recently been estimated to be 26.8 % among females aged 14–59 years [34]. Genital warts are typically flesh colored raised or flat lesions, often with a typical roughened keratinized head. Genital warts are diagnosed by examination and infection with the high grade oncogenic HPV is diagnosed by DNA PCR. HPV infection in many cases is self-limiting and the virus is cleared without the need for medical attention. In the case of genital warts, patients may request treatment with cryotherapy or topical treatments. Condoms provide some, but not total protection from HPV.

HPV Infection and Fertility

Studies of HPV and male fertility have tended to isolate types 16 and 18, the high-grade oncogenic viruses, as the viruses associated with male infertility. Studies have shown a significant association with asthenospermia [35], a reduced total sperm count [24] and an effect on some aspects of sperm motility. Though not significant, a trend towards impaired sperm function was seen in several studies [34–36]. In contrast other studies have seen no effect on semen volume, sperm concentration or motility, or any associated oligospermia or asthenospermia [36, 37]. It is unclear if there is a direct effect on the sperm or whether the presence of HPV alters the pH of the semen, thus impairing sperm motility [36]. There is conflicting data as to whether HPV causes psychological problems including sexual enjoyment and frequency of intercourse [38–41]. In practice we often see young men complaining of sexual dysfunction after a diagnosis of HPV infection has been made.

Trichomonas vaginalis

Trichomonas vaginalis, a member of the Trichomonadidae family, is an anaerobic, flagellated protozoan that lives in the human urogenital tract. It is the most common sexually transmitted infection worldwide with an estimated 173 million cases in 1999 [42]. The estimated prevalence in the USA is 3.1 % [43]. Infection tends to be asymptomatic, only causing symptoms in about 30 % of cases. The symptoms in men include dysuria, irritation in the urethra, or urethral discharge. Diagnosis can be made by culture, wet mount, NAATs (nucleic acid amplification tests), and point-of-care tests. Wet mount examination is less reliable in men compared to women. Staining methods should have confirmatory testing. In most cases treatment consists of immediate administration of 2 g of metronidazole.

Trichomonas and Fertility

The association is controversial. Some research has shown that the presence of Trichomonas was associated with reduced sperm motility and viability with a reduction in the percentage of normal morphology when compared to men without Trichomonas. Treatment significantly improved these parameters in 50 % of men after one dose of metronidazole [44]. In vitro mixing of sperm with Trichomonas showed reduced sperm activity [45]; it has also been shown that a proteinaceous substance produced by Trichomonas kills sperm rapidly [46]. Conversely a study by Daly showed no effect on sperm number or motility with the presence of Trichomonas in vitro [47].

Syphilis

Syphilis is a relatively common STD, with approximately 12 million new infections each year worldwide [48]. There is wide geographic variation in the rates of syphilis. In the newly independent states of the former Soviet Union, rates have risen dramatically since 1990 from an estimated 5–15 per 100,000 to 120–170 per 100,000 in 1999. More recent data from surveillance of syphilis in the USA showed that there were 45,834 reported cases of syphilis in 2010, at a rate of 14.9 per 100,000 [49]. The majority of these cases were in urban areas or the Southern states. In the UK, the rates of infectious syphilis (primary, secondary or early latent) peaked in 2005 and were 5.6 per 100,000 in 2011 [50].

Syphilis is caused by infection with *Treponema pallidum*. Transmission occurs through direct inoculation from an infectious lesion (through sexual contact including vaginal and anal sex, oral sex, and mutual masturbation), mother to child in utero and also rarely through blood and blood products.

For classification, stages and clinical presentation of syphilis *see* Table 5.3.

Diagnosis can be made in early syphilis by direct visualization of spirochetes from a syphilitic lesion via dark-ground microscopy. There is also specific *T. pallidum* PCR that can be performed from a swab taken from a chancre. Most commonly syphilis is diagnosed by serological tests. Screening consists of using an automated treponemal test, usually the EIA (enzyme immunoassay) for IgG, with or without IgM, and confirmation with TPPA (*T. pallidum* particle agglutination assay) or TPHA (*T. pallidum* hemagglutination assay). Nonspecific tests include VDRL and RPR. These are indicators of infectivity and are normally raised in early syphilis. The subsequent fall in RPR is an important marker of successful treatment.

Treatment is with antibiotics, most evidence supporting a penicillin-based regime. The length, dose, and delivery of treatment with repository penicillin are dependent on the stage of disease and clinical scenario. There are alternative regimes such as doxycycline. The CDC, British Association for Sexual Health and HIV (BASHH), and International Union against Sexually Transmitted infections (IUSTI) provide up-to-date treatment guidelines available online [51–53].

Syphilis and Fertility

Testing both partners for syphilis and treating as required is imperative before proceeding with any form of fertility treatment. The effects of infectious syphilis on the unborn child are devastating and include spontaneous abortion and still birth in 50 %, with mortality of infected infants being over 10 % [54].

Though a direct effect of syphilis on male fertility is not described in the literature, complications of syphilis can affect fertility. Tabes dorsalis is a known cause of erectile dysfunction. Gummatous lesions within the testis can lead to destruction of the testicular tissue. Chronic obliterative endarteritis and interstitial

Table 5.3 Classification, stages, and clinical presentation of syphilis

Classification	Stages		Time	Clinical signs and symptoms
Acquired	Early	Primary syphilis	3–90 days after inoculation (normally 14–21 days)	Chancre (single painless ulcer) regional lymphadenopathy
		Secondary syphilis	4–10 weeks after primary infection	Generalized rash (macular, papular, or maculo-papular) Generalized lymphadenopathy Mucocutaneous lesions Condylomata lata Headaches Cranial nerve palsies Optic neuritis Anterior uveitis Hepatitis Glomerulonephritis Periosteitis
		Early latent	Acquired less than 1 year previously (CDC) <2 years (WHO)	Serological evidence without clinical features
	Late	Late latent	Acquired more than 1 year previously (CDC) >2 years (WHO)	Serological evidence without clinical features
		Meninogovascular	2–7 years	Focal arteritis leading to infarction and presenting as a cerebral vascular accident
		Cardiovascular	10–30 years	Aortitis (commonly ascending aorta) Aneurysm formation Dilation of the aortic root Coronary ostial stenosis causing angina
		Neurological	10–25 years	General paresis (decline in memory and cognitive function, emotional liability and personality changes, psychosis, dementia, seizures, and hemiparesis) Tabes doralis (pain, paraesthesia, loss of reflexes, and sensory ataxia) Argyll Robertson pupils Optic atrophy
		Gummatous	1–46 years (average 15 years)	Destructive inflammatory granulomas occurring in any organ

(continued)

Table 5.3 (continued)

Classification	Stages	Time	Clinical signs and symptoms
Congenital	Early –	Presentation before 2 years of age	Hepatosplenomegaly Rash Generalized lymphadenopathy Hemorrhagic rhinitis Perioral fissures Osteochondritis Neurological involvement Non-immune hydrops
	Late –	Presentation >2 years after birth	Interstitial keratitis Hutchinson's incisors Mulberry molars Saddle nose deformity High palatal arch Saber shin Clutton's joints Neurological involvement Gummatous involvement

CDC Centers for Disease Control and Prevention, *WHO* World Health Organisation

inflammation can occur in congenital or tertiary syphilis, and lead to small, fibrotic testes [55]. Syphilitic epididymitis has also been described and classified into three forms: acute diffuse interstitial, chronic diffuse interstitial, and gummatous [56]. With a chronic inflammatory process there is fibrosis and scarring with the potential to cause obstruction of the epididymis. We postulate that, though rare, these complications and the psychological effect of having an STI may also have an adverse impact on male fertility.

Neisseria gonorrhea

Gonorrhea is caused by *Neisseria gonorrhea*, a gram-negative diplococcus. Worldwide there are an estimated 62 million people infected annually [57]. It accounted for 820,000 cases of STIs in the USA in 2008 [2]. Symptoms of genital infection include purulent discharge and dysuria. Infection can be asymptomatic, especially in the pharynx or rectum. Gonorrhea can cause conjunctivitis, epididymo-orchitis, prostatitis, or pelvic inflammatory disease through local spread or direct inoculation. Disseminated Gonococcal Infection (DGI) occurs in about 1 % of cases [57]. DGI commonly presents with a petechial or pustular rash, asymmetrical arthralgia, tenosynovitis, or septic arthritis. Rarely it can cause a perihepatitis, endocarditis, and meningitis.

Diagnosis is made by direct visualization on gram stain of a urethral, cervical, or rectal smear. It is then confirmed by culture. NAATs for gonorrhea are now widely used and are thought to have increased the diagnosis rate, especially in asymptomatic cases and extra-urethral sites.

A wide variety of antibiotics have been used to treat gonorrhea over the years. There have been issues with drug resistance. In view of this, it is always worth sending cultures for sensitivities whenever possible and following local guidelines on the use of antibiotics. Currently in the UK, ceftriaxone 500 mg IM injection is recommended for the treatment of gonorrhea. It is given with antibiotic cover for Chlamydia as 10 % of cases have both infections.

Gonorrhea and Fertility

Gonorrhea tends to cause an acute infective episode. The relationship between infection and infertility is due to the resultant PID in women. In men the subsequent scarring and obliteration of the epididymal canal following an acute infection is usually persistent even after cure. If bilateral, the infection can result in obstructive azoospermia [58].

Chlamydia trachomatis

Chlamydia trachomatis is a gram-negative, aerobic, intracellular bacterium. It is one of the most common sexually transmitted infections worldwide and the most commonly reported bacterial STI in England and the USA. Chlamydia is transmitted by sexual contact including the use of sex toys and also from mother to child. It can infect the cervix, urethra, rectum, pharynx, and conjunctiva. The majority of cases are asymptomatic. Male symptoms include urethral discomfort, pain on urination, urethral discharge, and testicular pain. The infection is normally confined to the urethra causing urethritis, but can ascend and cause prostatitis and epididymo-orchitis. NAATs are used widely to diagnose Chlamydia via a swab taken from the site of infection or first void urine sample (urethral infection). Other tests include culture, EIA, DFA (direct fluorescent antibody), and nucleic acid hybridization tests. Treatment is with a stat dose of azithromycin 1 g in most cases. Alternatives include doxycycline 100 mg bid for 1 week. If there is evidence of pelvic inflammatory disease or of ascending infection in the male (epididymitis, orchitis, or prostatitis), a longer course of antibiotics such as ofloxacin is recommended.

Chlamydia and Fertility

A common anxiety with a diagnosis of Chlamydia is the effect on a woman's fertility. Chlamydia is associated with pelvic inflammatory disease (PID) and female tubal infertility, though a recent study suggests the risk of developing PID

with untreated Chlamydia is low with a relative risk of 0.17 (0.03–1.01) $p = 0.07$ after 1 year follow-up. PID was, in fact, seen more frequently in Chlamydia negative women [59]. With regard to male infertility, the connection is even less clear. There are several theories as to how Chlamydia may affect male fertility. These include a direct effect of the Chlamydia, the presence of associated inflammation, or the development of anti-sperm antibodies triggered by Chlamydia. The research has been contradictory and is inconclusive. It has been shown that the presence of elementary bodies of *C. trachomatis* serovar E within the lab setting caused a significant decrease in motile sperm with an increase of dead spermatozoa [60]. The detection of Chlamydia in either semen or urine has been associated with a reduction in sperm numbers [61], reduction of the percentage of progressively motile sperm [62–65], and abnormal morphology and viability [65].

Chlamydia has also been shown to cause sperm DNA fragmentation that improves with treatment [64]. Chlamydia has not been shown to affect the percentage of immotile or viable sperm [62], and there are other contrasting studies that show no association with DNA fragmentation [63] or effect on sperm concentration, motility, and/or morphology [66]. The presence of *C. trachomatis* antibodies, therefore, has not been shown to be conclusively linked to infertility, although there are studies suggesting an association [67], and others showing that despite an associated inflammatory response, there was no effect on sperm parameters [68].

Male Accessory Gland Infections

Male accessory gland infections (MAGIs) include urethritis, epididymitis, orchitis, and prostatitis. These infections are potentially curable causes of male infertility, though studies so far have not been conclusive in showing an effect on sperm quality and male fertility. A study has shown that MAGI with abnormal semen quality as the only abnormality was seen in 1.6 % of infertile couples. Sperm motility and morphology showed improvement over time whether treated or not, and this improvement did not seem to enhance the probability of conception [69].

Urethritis

Urethritis is most commonly caused by infections such as *C. trachomatis*, *N. gonorrhea*, *Ureaplasma urealyticum* and *Mycoplasma genitalium*. Other less common causes are *T. vaginalis* and *Herpes simplex* virus. Urethritis can also be caused by allergic reactions and trauma. The main symptoms include pain on voiding and urethral discharge. Diagnosis is made on the clinical presence of mucopurulent or purulent discharge, $\geq$5 granulocytes per microscopic high power field (1,000×) on a urethral smear, a positive leukocyte esterase test on first-void urine, or microscopic examination of first-void urine sediment demonstrating $\geq$10

WBC per high-power [70]. Both CDC and BASHH guidelines recommend the use of a single dose of Azithromycin 1 g if gonorrhea is excluded on urethral gram stain.

A recent study found that there were more abnormalities of semen parameters in attendees of genitourinary medicine clinics, especially those patients with asymptomatic, Chlamydia negative, nonspecific urethritis as compared with men attending a General Practitioner (Family Physician) for the first check for possible infertility [71]. There have also been several studies looking at the effect of the bacterial pathogens that are associated with urethritis on sperm quality and fertility. A recent study showed that semen contaminations with *Mycoplasma* spp. and Chlamydia were associated with decreased sperm concentrations, with Mycoplasma having the highest adverse effect on sperm quality (concentration, motility, morphology, and DNA condensation). Unfortunately, despite successful antibiotic therapy, semen quality parameters did not improve at least up to 3 months after the therapy. Sperm chromatin integrity assessed by the presence of DNA breaks was not seen with these infections [72]. Also, when looking at the prevalence of these infections, there was no difference comparing fertile to infertile couples [73].

Epididymitis

Acute inflammation of the epididymis is most commonly caused by bacterial infection. A sexually transmitted infection such as Chlamydia or Gonorrhea is the most common cause in men less than 35 years of age. In older men, especially those with a history of bladder outlet obstruction, *Escherichia coli* is more common. Rarer causes of epididymitis include *Mycobacterium tuberculosis*. Noninfectious causes include Behcet's disease, urethral manipulation, following vasectomy and as an adverse effect of amiodarone. With any inflammatory process there is the risk of scarring and fibrosis. Though uncommon, bilateral occlusion of the epididymis is a cause of azoospermia and, therefore, male infertility.

Orchitis

Orchitis is defined as inflammation of one or both testes. It may be caused by a variety of viral and bacterial infections. Symptoms include tenderness or swelling in the groin or testes, as well as pain on intercourse or urination. Treatment is supportive, with treatment of any specific underlying cause if identified. Complications of orchitis include testicular atrophy and testicular infarction. Both conditions can impair testicular function and may have an adverse impact on fertility. Mumps occurring after puberty is commonly associated with unilateral or bilateral orchitis. This can cause reduced fertility in men.

Prostatitis

Prostatitis is classified into four distinct conditions by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). Acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain (this may be inflammatory or non-inflammatory), and, finally, asymptomatic inflammatory prostatitis are often found when investigating other urological conditions or fertility issues.

The impact of chronic prostatitis on male fertility has not been conclusively proven. Chronic prostatitis caused by *C. trachomatis* was shown in one study to result in significant differences in sperm concentration, motility, and morphology compared to the effect of prostatitis due to other uropathogens [74].

A study of 30 men, all with leucocytosis, who had undergone long-term treatment for chronic prostatitis with antimicrobials showed improvement or normalization of the sperm count in 70 % [75]. A study published in 1991 compared patients with a diagnosis of chronic abacterial prostatovesiculitis (current NIDDK classification of chronic prostatitis/chronic pelvic pain) to age-matched asymptomatic controls. All the patients in the prostatitis group had ultrasound evidence of chronic inflammatory changes. The study showed that patients in the prostatitis group had an increased incidence of disturbed sperm quality and azoospermia, though some were normospermic. Not all patients in the prostatitis group had leukospermia and the degree of the leukospermia could not predict the extent of the disturbance in semen quality [76]. Psychological stress is common in patients with prostatitis, with 43 % of men with symptomatic prostatitis complaining of erectile dysfunction and 24 % reporting low libido [77], thus impacting further the ability to conceive.

Conclusion

The role that STIs play in male infertility is not fully understood. Many studies to date have shown conflicting results and the differing techniques used to analyze sperm makes comparison of the various studies difficult. The lack of markers for previous infection in some STIs adds to these research difficulties. For example, we cannot test for previous Gonorrhea infections. As for Chlamydia, serum IgG for Chlamydia is not specific for genital infection. IgA in the semen may be a more specific test for previous genital infection. Finding IgG antibodies to HSV 1 and 2 does not imply active disease.

Now that the WHO has produced an internationally agreed definition of sperm abnormalities and with the improvement in diagnostic tests, hopefully, we can expect some of the questions posed by research to date to be answered in the near future. It will remain difficult to determine which of the various factors may be relevant to the possible development of male infertility for each specific STI. Is it an

effect related to the specific pathophysiology of the organism, or to the inflammatory response provoked, or to the nonspecific damage to the male genital tract? Is it mediated by changes to the sperm or the seminal fluid? What part does the psychological impact of the concept of infection play in the function of the man or his partner? We must not forget that various multiple and complex factors play a part in the normal process of conception, which evidentially differ even at an individual level, providing ample opportunity for disturbance by the pathophysiology of disease.

In the meantime it is always prudent to screen and treat those at risk of STIs. In infertile couples the screening and treatment of any underlying pathology is a sensible approach in order to avoid where possible both any impact on fertility and also the known complications of pregnancy.

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