tween chronic prostatitis syndrome and pelvic venous disease: a survey of 2,554 urological outpatients. Eur Urol 37:400–403


Tomlinson MJ, Barratt CLR, Cooke ID (1993) Prospective study of leukocytes and leukocyte subpopulations in semen suggests they are not a cause of male infertility. Fertil Steril 60:1069–1075


II.2.4 Urethritis, Sexually Transmitted Diseases (STD), Acquired Immunodeficiency Syndrome (AIDS)

F. R. Ochsendorf

Summary

According to the present data, urethritis poses no problem for male fertility. In chronic infections, for example gonorrhoea, urethral strictures and epididymo-orchitis are possible. Chlamydia trachomatis and Neisseria gonorrhoeae can lead to pelvic inflammatory disease of the female partner and tubal obstruction. Depending on the local prevalence some sexually transmitted disease (STD) agents can impair male fertility if not adequately treated. Any STD increases the chance of transmission of human immunodeficiency virus (HIV). HIV infection is associated with infectious semen and the risk of transmission of the virus. Men who are seropositive only and do not have full-blown AIDS often present with normal semen parameters. Their endocrine and exocrine testicular functions are, however, impaired with progression of the acquired immunodeficiency. Reproduction in HIV-serodiscordant couples is possible by special sperm washing procedures and testing of the samples prior to assisted reproductive techniques.

II.2.4.1 Introduction

A common feature shared by STD is that the causative microorganisms are labile in inanimate environments. Therefore, they are only transmitted via intimate contact. They are summarized in Table II.2.4 and Chap. I.6.1. Due to their shared mode of transmission, several of these agents may be transferred together, so the diagnosis of one STD prompts the search for others.
Table II.2.4. The most common microorganisms causing urethritis, their diagnoses and treatment. The percentages are taken from the literature; in case of strong variance, the maximal and minimal numbers are given in parentheses (from Gall et al. 1999; Elsner et al. 1987; Heise 2001; Kohl 2001)

<table>
<thead>
<tr>
<th>Microorganism and incubation time</th>
<th>Frequency (%)</th>
<th>Detection method</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria gonorrhoea 1–6 (–14) days</td>
<td>0.4 – 9– 18</td>
<td>Culture (Thayer-Martin selective medium; fast transport!); DNA hybridization (first-void urine)</td>
<td>Once: spectinomycin 2 g or ceftriaxone 0.25 g i.m. alternatively (p.o.): cefixim 400 mg or ciprofloxacin 500 mg or ofloxacin 400 mg or azithromycin 1 g</td>
</tr>
<tr>
<td>C. trachomatis 7–21 days</td>
<td>15 – 26</td>
<td>Ag-detection (direct immunofluorescence, EIA), DNA amplification (PCR; LCR)</td>
<td>Once: azithromycin 1 × 1000 mg or 7 days: doxycycline 2 × 100 mg; alternative: (7 days p.o.): tetracyclines 4 × 500 mg or erythromycin 4 × 500 mg or ofloxacin 2 × 300 mg</td>
</tr>
<tr>
<td>Mycoplasma Ureaplasma urealyticum Mycoplasma hominis</td>
<td>10–21</td>
<td>Culture (special medium)</td>
<td>As Chlamydia</td>
</tr>
<tr>
<td>Mycoplasma genitalium (Deguchi and Maeda 2002) Pathogenic bacteria (Entero- coccius, beta-haemolyising streptococci, E. coli, Staphylococcus aureus)</td>
<td>18–45</td>
<td>Special culture (no routine method available)</td>
<td>7 days doxycycline 2 × 100 mg/day; alternative: macrolides, new chinolone</td>
</tr>
<tr>
<td>Trichomonas vaginalis 4 days to 3 weeks</td>
<td>0.4–1</td>
<td>Urine sediment of first-void urine</td>
<td>Once metronidazole 2 g p.o. or tinidazole 2 g p.o.</td>
</tr>
<tr>
<td>Herpes simplex Single cases</td>
<td>Only if no therapeutic effect: culture, antigen detection or PCR</td>
<td>Aciclovir 5 × 200 mg p.o. 5–7 days</td>
<td></td>
</tr>
<tr>
<td>Candida Single cases 3</td>
<td>Only if no therapeutic effect: culture</td>
<td>Topical imidazole derivative; alternative: p.o.: fluconazole 1 × 150 mg p.o. or ketoconazole 2 × 200 mg 5 days</td>
<td></td>
</tr>
<tr>
<td>No agent demonstrable Possible causes: False-negative test Functional irritation Traumatic urethritis Tumours of the urethra HPV infection General disease</td>
<td>–26</td>
<td>Repetition of microbiologic tests, history</td>
<td>History</td>
</tr>
</tbody>
</table>

STDs can lead to pelvic inflammatory disease (Ankum et al. 1996), ectopic pregnancy, infertility, chronic pelvic pain, genital lesions, genital neoplasms, adverse pregnancy outcomes, immune system dysfunction, liver disease, gonococcal sepsis and even death; so, they have a considerable impact on the health of men and women. Even if the disease does not cause definite impairment of sperm parameters, for example Chlamydia trachomatis infections in men, it may be transferred to the female partner and so has considerable impact in women, such as pelvic inflammatory disease resulting in tubal occlusion (Sulak 2003).

There are studies reporting a positive history concerning STDs in 45% of infertile patients (Schulenburg et al. 1993), while others did not find associations between prior urethral discharge or dysuria and subsequent semen quality (Oldereid et al. 1992). A higher percentage of STD agents was reported in infertile men and women than in controls (Rodriguez et al. 2001). It is likely that the prevalence of STDs, the availability of health services, and the time and mode of STD treatment in a given population are all factors influencing the role of these infections in male infertility (Cates et al. 1985; De Schryver and Meheus 1990; Bambra 1999; Jansen et al. 2003; Orroth et al. 2003; Bayasgalan et al. 2004). There are several reviews addressing these questions in more detail (Keck et al. 1998; Comhaire et al. 1999; Paavonen and Eggert-Kruse 1999; Sulak 2003).

II.2.4.2 Urethritis

II.2.4.2.1 Pathogens

Urethritis can be caused by several pathogens (Table II.2.4; Elsner et al. 1987; Gall et al. 1999; Heise 2001; Kohl 2001; Deguchi and Maeda 2002). The most rele-
vant are gonorrhoea, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis* (Table II.2.4). Urethritis caused by mechanical trauma is unrelated to infertility. Ascension of gonococci is estimated to occur in about 1% of infected patients.

### II.2.4.2.2 Clinical Presentation

The symptoms are variable. In acute urethritis, the patient notices a urethral discharge and dysuria. Others have no symptoms or are symptom-free throughout the day and only notice a drop of pus in the morning prior to the first voiding of urine. Sometimes the glans or meatus urethrae may present with some redness as a sign of inflammation.

### II.2.4.2.3 Diagnosis

The demonstration of >15 granulocytes in the sediment of the first 3 ml of urine (400× magnification) is regarded as pathognomonic for an acute inflammation of the urethra (Schiefer 1998). The definite diagnosis is made by demonstration of the pathogenic agent [culture, direct immunofluorescence, enzyme immunoassay (EIA) and nowadays molecular methods such as polymerase chain reaction (PCR) or ligase chain reaction (LCR); see Table II.2.4]. These tests have different sensitivities and specificities (Watson et al. 2002).

### II.2.4.2.4 Relevance

The question of whether urethritis leads to male infertility is discussed controversially. It is biologically plausible that gonorrhoea and/or *Chlamydia* could cause male infertility. There is clinical and pathologic evidence linking these pathogens to urethritis, linking urethritis to epididymo-orchitis, and linking epididymo-orchitis to infertility. A retrospective analysis of the literature, however, could not substantiate whether these pathogens alter sperm characteristics. Methodological problems were thought to be responsible (Ness et al. 1997). As yet there are no prospective controlled studies definitely proving this association. Urethral stricture is another possible complication of urethritis, mainly due to gonococci (Bewes 1973).

**Gonorrhoea**

The seroprevalence of *N. gonorrhoeae* ranged from 3% to 31% in different risk groups (study in Mexico; Cravioto Mdel et al. 2003). These rates are different in other countries (Dougan et al. 2004).

Especially in Africa infertility due to tubal obstruction appears to be a relevant issue (Meheus et al. 1986). In men urethral strictures may occur (Osoba 1981; Fievet et al. 1987). Most strictures are seen in the posterior urethra, where fibrosis and narrowing may extend from a short length of under 5 mm to well over 10 cm. A wide variety of initial complaints and complications occurs. When the patient presents in acute retention or with a history of difficult micturition, the diagnosis is easy. However, when stricture is the underlying cause of perianal abscess, gangrene of the scrotum caused by extravasation, uraemia or hypertension, hernia or rectal prolapse, urinary infection, or elephantiasis of scrotum with multiple fistulae, diagnosis may be difficult. A careful history is helpful, particularly if previous gonorrhoea is involved. The definite diagnosis is made by urethrography and urethroscopy (Bewes 1973). In Western countries such as Scotland, however, gonorrhoea is not a relevant cause of urethral strictures (McMillan et al. 1994). It was proposed that a decline in subfertility in Sweden could be attributed to the eradication of gonorrhoea (Akre et al. 1999), a view not shared by others (Jensen et al. 2000).

In men with asymptomatic gonorrhoea no differences in spermogram parameters were found before and after treatment in comparison to a control group, with the exception of lowered citrate concentrations (Perez-Plaza et al. 1982). However, a follow-up investigation of men with proven fertility after having had gonorrhoeal urethritis and unilateral epididymo-orchitis showed that 2 years later only 21% produced semen considered adequate for conception. Although the lesions were clinically confined to one testis, testicular biopsy samples showed damage in both testes. So gonorrhoea can lead to oligo- and azoospermia (Osegbe 1991). Others reported an increased incidence of anti-sperm antibodies after gonococcal urethritis (Shahmanesh et al. 1986). Gonococci survive cryopreservation in liquid nitrogen, which has to be taken into account for the screening of sperm donors (Sherman and Rosenfeld 1975; Glander et al. 1986).

During routine semen analyses of asymptomatic males no screening for gonococci routinely takes place in a low prevalence setting. It was reported that dilution of semen (1:2 with saline) enhances the detection rates of *N. gonorrhoeae* (undiluted: 0 positive; diluted: 9/68 positive; Vicari et al. 1986). The same authors reported positive gonorrhoea cultures in 111/785 (14%) men in an andrologic outpatient clinic (Vicari et al. 1991). So the screening apparently has to be adjusted to local prevalence of the disease.

The relevance of *N. gonorrhoeae* lies in its capacity to lead to urethral strictures and testicular damage as a consequence of epididymo-orchitis in the male as well as ductal inflammation and obstruction in the female.
**Chlamydia trachomatis**

The role of *Chlamydia trachomatis* as a cause of male infertility is discussed controversially (Krause and Bohring 2003; Gonzales et al. 2004). There is no doubt that *Chlamydia trachomatis* is a frequent pathogen in male genital inflammation and that this organism is rarely present in healthy men. *Chlamydia trachomatis* causes inflammation of the male urethra and the epididymis. However, it remains unresolved and unclear whether it causes prostatitis and infections of the seminal vesicles (Weidner et al. 1999, 2002).

*Chlamydia trachomatis* antigen or DNA is easily demonstrable in urethral swabs and the urine. The sensitivities of DNA amplification techniques (LCR, PCR, gene probe) in first-void urine were higher (85 – 96%) than in cervical swabs (84 – 88%; the same will hold true for urethral swabs) and yielded better results than an EIA (urine 38%, swab 65%). Especially in low prevalence populations the molecular methods are more effective at detecting asymptomatic chlamydial infections than conventional tests (Watson et al. 2002). *Chlamydia trachomatis*, however, cannot be reproducibly demonstrated in secretions of the male accessory glands, including semen.

Sero logic studies can be useful in epidemiologic investigations. In these studies an association was found between the detection of immunotype-specific *C. trachomatis* antibodies and subfertility both in men and women. So a previous *C. trachomatis* infection appears to be associated with subfertility in male or female partners of a given couple (Karinen et al. 2004).

The role of *Chlamydia* serology as a marker of recent infection is a matter of debate. Former investigations used tests that could not discriminate between *C. trachomatis* and *C. pneumoniae*. Different test systems yielded conflicting results. Thus determination of chlamydial antibodies in serum or semen does not conclusively indicate a current infection with *C. trachomatis*. The profile of these antibodies after treatment is unknown. Some authors found higher antibody prevalences of *Chlamydia trachomatis* antibodies in infertile men and associations with heat-shock proteins (Schuppe et al. 2003), others with inflammatory markers (Wolff et al. 1991; Ochsendorf et al. 1999).

Observations are available indicating that *Chlamydia* can enter human spermatozoa (Erbengi 1993), that they may induce antibody production (Shahmanesh et al. 1986; Soffer et al. 1990; Witkin et al. 1995a, b) and may be associated with oxidative stress (Segnini et al. 2003) and inflammation (Hosseinzadeh et al. 2004). However, there are no conclusive studies showing that men infected with *C. trachomatis* are less fertile than uninfected men (literature in Krause and Bohring 2003). Furthermore, sperm functions are not impaired (Vigil et al. 2002). So sperm apparently act as vehicles to transport the pathogen to the female.

There is no question that male genital chlamydial infections are a threat to female genital organs, because *C. trachomatis* infection of the female genital organs may be deleterious to female fertility mainly due to tubal occlusion. This has been repeatedly demonstrated (Eggert-Kruse et al. 1990, 1996; Paavonen and Eggert-Kruse 1999; Krause and Bohring 2003; Mardh 2004). So *C. trachomatis* primarily has to be regarded as a threat to female infertility.

**Mycoplasmas**

Mycoplasmas include *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Mycoplasma genitalium*. While the first two germs can colonize the urethra without causing symptoms, the latter was suspected to be a major cause of urethritis and possibly cervicitis (Uusakula and Kohl 2002). It was suggested that female partners should be screened for these microorganisms in order to detect them in the male genital tract (Trum et al. 2000). The incidence of *U. urealyticum* in the semen of fertile and infertile men was reported to range between 7 and 42% (Reichart et al. 2000). A higher incidence was reported in the semen of infertile men (38% to 9% in controls) (dXu et al. 1997). *U. urealyticum* was suspected to cause chronic prostatitis (Badalyan et al. 2003). *U. urealyticum* and *M. genitalium* can attach to spermatozoa, be transported in the female genital tract and can cause female genital disease (Taylor-Robinson 2002; Svenstrup et al. 2003).

In in vitro fertilization (IVF) programmes *M. hominis* was found in 2 – 12% and *U. urealyticum* in 17 – 29% in semen (Hill 1990; Witkin et al. 1995b). The demonstration of a mycoplasma infection was not related to a change in sperm parameters (Soffer et al. 1990) or poorer IVF outcome if prior treatment with tetracyclines had been performed (Witkin et al. 1995a, b). It was suggested, however, that this infection can cause embryo loss without necessarily affecting semen quality. One possible mechanism is unstable chromatin. In vitro incubation resulted in time- and dose-dependent chromatin decondensation and DNA damage of sperm cells. In vivo these effects could be reduced by doxycycline therapy (Reichart et al. 2000).

Thus *U. urealyticum* may cause infertility via deleterious effects on sperm chromatin and DNA, leading to impairment of embryo development. The exact role of these microorganisms, however, has still to be elucidated.

**Trichomonas vaginalis**

Protozoan infections of the male genital tract are rare and only a few species of parasites are involved (Marti-
T. vaginalis is the most common agent (~120 million new cases worldwide; Crosignani et al. 1992). Recently it was shown that the incidence in men may be underestimated if only one specimen was used to screen for this agent. Compared to first-void urine and urethral swabs, semen proved to be the most sensitive single specimen (in 25% only semen positive) for the detection of T. vaginalis (Kayedos-Daniels et al. 2004). In areas with a high prevalence of trichomoniasis, the addition of metronidazole to the syndromic management of male urethritis is recommended (Price et al. 2003). In women no differences in the detection rates of T. vaginalis between fertile and infertile women were reported (Okonofua et al. 1995). However, it was stressed that trichomoniasis may play a role in the development of cervical neoplasia, postinfective infections and adverse pregnancy outcomes, and as a factor in atypical pelvic inflammatory disease and infertility (Soper 2004).

A higher seminal contamination with Trichomonas was found in infertile men compared to fertile men (47% to 30%) as well as a higher viscosity and sperm agglutination. A significant improvement in semen characteristics was found in 50% of patients 1 month after treatment with metronidazole (Bornman et al. 1992b). Others could not confirm detrimental effects of T. vaginalis on sperm motility (Daly et al. 1989). No detrimental effects on sperm–mucus interaction were found (Egbert-Kruse et al. 1987). T. vaginalis does not survive cryopreservation of spermatozoa (Glander et al. 1986).

Trichomoniasis might cause reversible infertility in men, although the actual role of T. vaginalis infection in infertility has not yet been clearly defined (Martinez-Garcia et al. 1996; Soper 2004).

### 2.4.3 STD

Agents that are sexually transmitted are summarized in Chap. I.6.1, Table II.2.4. Some agents are not listed there as they are not associated with male infertility such as scabies or human papilloma virus infections. STDs are reviewed in several publications (Moskowitz and Mel linger 1992; Radcliffe 2001; Center of Disease Control and Prevention 2002; Sulak 2003). It was concluded that STDs are less important for men than for women with regard to fertility (Westrom 1994). Studies on large cohorts of men showed that there is no increased rate of antisperm antibody production in men attending STD clinics (Hargreave et al. 1984). So this mechanism appears not to be relevant.

The prevalence of STDs differs worldwide with higher incidences in developing countries (De Schryver and Meheus 1990). Furthermore the pattern changes from year to year, with a decrease in the 1990s during the HIV epidemic and a current rise in incidence (Dougan et al. 2004).

About two-thirds of STDs affect individuals younger than 25 (Braverman 2000). This sexually active population may have long-term negative sequelae, such as infertility, chronic pelvic pain and cancer; so, educational strategies are needed for their prevention (Wilken and Rosler 1985; Stone 1990; Workowski et al. 2002). This is sometimes hampered by fragmented responsibilities for STD and infertility services (Hardon 2003).

Human papilloma virus was demonstrated on the skin of about 13% of men attending an infertility clinic as well as in the semen of men with and without genital warts (Green et al. 1991; Pakendorf et al. 1998). Transmission from the woman to the man appears to be rather inefficient. HPV type 16 DNA and RNA (25% and 8% of randomly selected patients) as well as type 18 DNA and RNA (46% and 21%) were detected in sperm cells (literature in Dejucq and Jégou 2001). The incidence of asthenozoospermia was reported to be significantly higher in patients with HPV in their semen (Lai et al. 1997).

Syphilis incidence in an andrological outpatient department was reported to be 3–8% in South Africa (Bornman et al. 1992a). This is important from an epidemiological point of view: even if Treponema pallidum does not directly impair male infertility it demonstrates that patients are at risk for other STDs, especially HIV infection.

Today one main impact of STDs is their potential to increase the rate of HIV transmission. This has been clearly proven and reviewed. Therefore, the treatment of STDs is not only relevant to the prevention of long-term negative consequences for fertility but also to the prevention of HIV spread (Passey 1996; Ping et al. 2000; Aral 2001; Pilcher et al. 2004).

Finally, STD agents have to be taken into account during assisted reproductive techniques (Diani 1999) and in sperm donor programmes. Again the regional variation of STDs explains the large variations in reported incidences (Craig et al. 1997; Olutunbosun et al. 1998; Wortley et al. 1998).

### 2.4.4 HIV

The first reports about unusual deaths in homosexual men were published in 1981. Within months an acquired immunodeficiency was identified. In 1983 a virus as the probable cause of this acquired immunodeficiency syndrome (AIDS) was isolated and in the following years the causal link was proven (literature in: Hoffmann and Kamps 2004 or www.HIV.net, www.hivmedicine.com). One main goal is the prevention of further spread of the disease. At present, intravaginal topical formulations of anti-HIV agents or microbicides to
preventing the mucosal and perinatal HIV transmission are being developed. These agents should be capable of attacking HIV from different routes: directly inactivating HIV, preventing HIV from attaching to, entering or replicating in susceptible target cells as well as preventing dissemination from target cells present in semen or the host cells that line the vaginal wall (D’Cruz and Uckun 2004).

In the first years of the HIV epidemic problems other than reproduction had to be addressed. The wish for an own child was opposed by concerns about possible infections of the partner as well as the prognosis of the disease. Today, HIV infection is a chronic disease, so couples will be seen in greater numbers for preconception counselling. This involves a multidisciplinary approach to ensure that a couple is fully informed. The criteria to offer treatment or not should be based on the same criteria that are applied to couples who are affected by other chronic diseases. Medical treatment is dependent on the unique circumstances of each couple (Williams et al. 2003).

It is possible to help couples by using different methods of assisted reproduction. Until the middle of 2003 more than 1800 couples were treated in about 4500 cycles and about 500 children were born in Europe (Sonnenberg-Schwan 2004).

Infection with HIV has different influences on reproductive medicine: the function of the reproductive organs, ethical issues, prevention of spread to the child and safety issues for the laboratory personnel (Ethics Committee of the American Society for Reproductive Medicine 2004).

II.2.4.4.1 Effects of HIV on the Function of Male Reproductive Organs

Testis

The most relevant sources of HIV in the male reproductive tract are infected leukocytes (lymphocytes, monocytes, macrophages) (Dulioust et al. 1998). Vasectomy does not influence the amount of free virus in seminal plasma (Krieger et al. 1998). Controversy surrounds whether the virus also infects spermatozoa (Dejucq and Jégu 2001).

It was shown that testicular macrophages express CD4, CCR5 and CXCR4 thus allowing entry of HIV into these cells and providing a reservoir (Habasque et al. 2002).

Proviral DNA was detected in the nuclei of germ cells at all stages of differentiation in the testes of HIV-positive men by in situ PCR hybridization. The presence of provirus was not associated with germ cell damage, spermatogenesis was normal and a very mild local immune response was observed (Mucaccia et al. 1998b). According to electron microscopy, HIV can attach to the surface of spermatozoa and enter these cells through the intact plasma membrane (Bagasra et al. 1994) probably by an alternative receptor (the GalAG) (Piomboni and Baccetti 2000) or a 160-kDa sperm protein (Bandivdekar et al. 2003). Others could not confirm this (Pudney et al. 1998). It is possible to generate HIV-free spermatozoa fractions by washing procedures, which is an argument against infection of motile spermatozoa by this virus (Semprini and Fiore 2004).

In prostate and testis tissues T lymphocytes were the predominant cells infected with HIV-1. So it was concluded that HIV-1 in seminal plasma is derived from the prostate, while HIV-1-infected cells in semen originate mostly from the rete testis and epididymis (Paranjpe et al. 2002).

Several endocrine and testicular dysfunctions have been reported in men infected with HIV, depending, in part, on the stage of the disease. Hypogonadism was shown to be common in HIV disease. It was suggested that the weight loss observed in full-blown AIDS may be a result of lowered testosterone levels (Dobs et al. 1988; Villette et al. 1990; Schurmeyer et al. 1997). A significant association was observed between testicular atrophy and body mass index (BMI) ($P = 0.0496$). Thus, underweight patients with HIV infection were 3.52 times more likely to have testicular atrophy than those with acceptable body weight (Mhawech et al. 2001).

Studies showing that testosterone replacement in HIV-infected patients with weight loss and low testosterone levels can improve muscle mass, effort-dependent strength, lean body mass and other symptoms of hypogonadism are in favour of this argument (Bhasin et al. 1998; Bhasin and Javanbakht 1999). If reproduction is planned, however, it has to be taken into account that reversible azoospermia may result from testosterone therapy (Pena et al. 2003). Furthermore it was shown that about one-third of HIV-infected men attending gyms used anabolic steroids (Bolding et al. 2002).

In AIDS patients orchitis, hypogonadism, oligozoospermia or azoospermia have been reported (Dobs et al. 1988; Pudney and Anderson 1991; Poretsky et al. 1995). Furthermore in some cases testicular germ cell tumours or lymphoma were found. The incidence of testis tumours was 57 times higher than the average US incidence (0.2% in 3015 HIV-positive men to 0.0035% in the normal population; Tessler and Catanese 1987).

Discussed mechanisms for the mode of action of HIV on the testis include unspecific accompanying deterioration of functions due to the chronic debilitating illness and cachexia of the patients or synergistic effects of opportunistic infections such as cytomegalovirus (CMV), Mycobacterium avium-intracellulare or Toxoplasma gondii in the testis. As only every third patient had such infections but demonstrable testis changes, these infections were probably not the main cause (De Paepe et al. 1990). A change in the hypothe-
Hypogonadism probably results from a decrease in Leydig cell number and a lymphocyte infiltration and fibrosis of the interstitial testicular tissue (Dalton and Harcourt-Webster 1991; Pudney and Anderson 1991). In the testis several changes were described and a classification system for them was proposed (De Paep and Waxman 1989; Yoshikawa et al. 1989). The authors found Sertoli cell only syndrome (42%), germ cell generation (27%), peritubular fibrosis associated with tubular hyalinization (15%), maturation arrest (12.5%) and normal appearance (3%). In addition, spermatogenic arrest at various points, degenerating germ cells and block in the epithelium were described by others (Shevchuk et al. 1998). Prolonging the survival by antiretroviral drug therapy was associated with a shift in the histologic findings toward more pronounced loss of germ cells (Shevchuk et al. 1999).

Thus it appears that direct local action may be responsible for this observed damage within the gonads. There are several lines of evidence for this statement: Da Silva et al. 1990 detected the HIV p17 protein in the testis by immunohistochemistry. Later, HIV-infected cells of the lymphocytic/monocytic type were found in the seminiferous tubules and interstitium of the testis as well as semen (Pudney and Anderson 1991). With PCR HIV-1 DNA was found within testicular germ cells in spermatogonia, spermatocytes and some spermatids (Nuovo et al. 1994). Others demonstrated the presence of HIV DNA in the nuclei of spermatogonia and germ cells at all stages of differentiation (Mucciaccia et al. 1998a, b). The mere presence of the provirus was not associated with impaired spermatogenesis in asymptomatic HIV-positive men. In AIDS patients, however, spermatogenesis was arrested and only few infected spermatogonia and spermatocytes were found (Mucciaccia et al. 1998a). In about 25–33% of the residual germ cells in the testes of AIDS patients, HIV DNA could be found but not in the testes of adolescent boys who had acquired HIV in utero (Shevchuk et al. 1998).

So the HIV infection impairs exocrine and endocrine testicular functions with progression of the disease.

**Ejaculate**

In symptomless HIV-positive men semen parameters within the normal range are found. With progress of the disease more defects are found, particularly in strict criteria of sperm morphology. Lower CD4+ cell counts (<200 mm³) were associated with significantly lower motility, lower than normal sperm morphology by strict criteria, more spermatids in semen, and higher percentages of teratozoospermia, oligoasthenoteratozoospermia and leukocytospermia. Healthier men, based on clinical categories, had significantly more normal-shaped spermatozoa and fewer had azospermia, oligoasthenoteratozoospermia or leukocytospermia. In AIDS patients, grossly abnormal sperm and pyospermia was reported (Muller et al. 1998; Nicopoulos et al. 2004). There were no differences in any parameters in those taking antiretroviral medication (Nicopoulos et al. 2004).

Others reported reduced semen volume, lower percentages of rapidly progressive motility, total sperm count and increased concentrations of non-spermatic cells (Dulioust et al. 2002).

In one sperm donor semen was analysed before and after HIV infection. Semen volume, sperm motility and the percentage of sperm with normal morphology were reduced after HIV positivity. A disturbed function of seminal vesicles and prostate gland could explain the decreased volume as well as the more viscous semen found in HIV-infected subjects (Dondero et al. 1996; Van Leeuwen et al. 2004). Sperm alterations found today are attributed to effects of antiretroviral therapy (Dulioust et al. 2002; Barboza et al. 2004).

**II.2.4.4.2 Ethical Issues**

A recent update on the ethical issues associated with reproduction in HIV-positive patients concluded that HIV infection is not yet curable, but treatable. It has to be classified as a chronic disease due to the significant advances in HIV treatment, which delay the onset of AIDS in many, but not all, infected persons. The potential for HIV-positive persons to have uninfected children and not transmit the virus to their partners has been substantially enhanced. So both HIV-infected persons and health-care providers share responsibility for the safety of the uninfected partner and the potential offspring. It was recommended that couples requesting assistance should have their own genetically related child seek care at institutions with the facilities that can provide the most effective evaluation, treatment and follow-up. As an alternative, donor semen, adoption or not having children have to be considered (Ethics Committee of the American Society for Reproductive Medicine 2004).

**II.2.4.4.3 Reproduction in Discordant Couples**

In a serodiscordant couple the female partner has a 0.1–0.2% risk of acquiring HIV per act of unprotected
intercourse (Mastro et al. 1997). This is dependent on the viral load in semen: it was calculated that the probability of HIV-1 transmission is 1/100 when semen contains 100,000 copies of HIV RNA and 3/10,000 with 1000 copies of HIV RNA in semen (Chakraborty et al. 2001). So attempts to conceive naturally carry a serious risk for the uninfected woman or child (Mandelbrot et al. 1997). The problems and unresolved questions of assisted reproduction in this situation are reviewed elsewhere (Englert et al. 2004).

During the initial consultation both partners should be counselled. This should include: information concerning diagnostics, therapy options, information on the psychosocial and economic situation and future perspectives of the couple, the family, and support through families and friends. It has to be stressed that the chances of HIV transmission are extremely improbable, but not impossible, and that a successful result of therapy, i.e. birth of a healthy child, cannot be guaranteed. Also the alternatives, i.e. the decisions of not having children, adoption or donor semen, have to be discussed.

If the couple opts for reproductive measures, an interdisciplinary approach is recommended (general medical diagnostics including infectiology, gynaecological and andrologic workup). Contact with an experienced centre with facilities for sperm preparation and HIV testing has to be established. The costs and insurance coverage of the planned procedures, which are different everywhere, have to be considered.

Psychosocial counselling is very important. Up to one-third then decide against children. If not discussed properly frustrations could lead to unprotected intercourse. In addition, comorbidities, such as drug abuse, can be detected (Sonnenberg-Schwan 2004).

**HIV Infection of the Man**

Depending on the semen quality spermatozoa can be used for intruterine insemination, IVF or intracytoplasmic sperm injection (ICSI). The semen has to be washed free of HIV and the success of this procedure has to be controlled prior to use (Hanabusa et al. 2000; Dunne et al. 2003; Weigel 2003; Bujan et al. 2004; Garrisdo et al. 2004; Nicopoulos et al. 2004). Potent antiretroviral therapy decreases the HIV load in semen and thus can be additionally used (Vernazza et al. 2000; Williams et al. 2003).

The spermatozoa are prepared using a gradient technique such as Puresperm (Nicadon, Sweden), which is diluted to 45% and 90% using a semen buffer medium. The ejaculate is layered over the prepared density gradients and centrifuged at 200 g at room temperature for 20 min. The supernatant is then aspirated, the sperm pellet removed, resuspended in fresh media and centrifuged again for 10 min. The washing procedure is repeated twice more. Then a swim-up procedure is done. An aliquot of washed spermatozoa is subsequently tested for detectable HIV RNA [for example, a nucleic acid-based sequence amplification (NASBA) assay such as Biomérieux]. In one study about 5% of NASBA tests were positive after this procedure (Nicopoulos et al. 2004).

**HIV Infection of the Woman**

Here a self-insemination could be tried at the optimum time point of the cycle. An inverted spermicide-free condom, a cervical cap, a vaginal applicator or a syringe may be used.

If assisted reproduction is necessary the experience to date points to a limited success rate (Ohl et al. 2003).

**II.2.4.4.4 Safety Issues of the Laboratory Personnel**

Only a few occupational transmissions of HIV have been reported. If standard precautions to prevent infectious disease transmission are taken, the risk of virus transmission to lab personnel is very small. In most cases nurses and laboratory technicians accidentally inoculated themselves with a patient's blood by a needlestick or were contaminated with bloody fluid and had significant mucocutaneous exposure (http://www.cdc.gov/niosh/topics/bbp/emergnedl.html, http://www.cdc.gov/ncidod/hip/Needle/needle.htm).

**References**


II.2 Mechanisms of Dysfunction and Pathology


cence virus and hepatitis C virus serodiscordant couples. Hum Reprod 19:2381 – 2586


mYdia trachomatis infection on male fertility. Andrologia 36:1 – 23


Lai YM, Yang FP, Pao CC (1997) The effect of human papillo-


Moskowitz MO, Mollinger BC (1992) Sexually transmitted dis-

Muciacia B, Filippini A, Ziparo E, Colelli F, Baroni CD, Stefa-
ni M (1998a) Testicular germ cells of HIV-seropositive asymptomatic men are infected by the virus. J Reprod Im-
munol 41:81 – 93


Ness RB, Markovic N, Carlson CL, Coughlin MT (1997) Do men become infertile after having sexually transmitted ure-

Nicozopoulos JD, Almeida PA, Ramsay JW, Gilling-Smith C (2004) The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemina-
tion following sperm washing. Hum Reprod 19:2289 – 2297

Nuovo GJ, Becker J, Simsir A, Margiotta M, Khalife G, Shev-
chuk M (1994) HIV-1 nucleic acids localize to the sperma-

ma are C. trachomatis specific and associated with an in-
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II.2.5 Disorders of Blood Flow: Arterial and Venous/
Sexual Dysfunction and Varicocele

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Summary

- Endothelial damage is the key disorder in vasculogenic organic erectile dysfunction (ED).
- Middle-aged men with ED should be screened for vasculogenic risk factors.
- Our improved understanding of endothelial damage will facilitate the development of a marker of endothelial damage, which, if developed, could have a significant impact on the diagnosis of men’s vascular disorders.
- Varicocele alters the dynamics of testicular circulation and this, in turn, damages spermatogenesis and endocrine function of the testis.

- In cases of testicular torsion there is reduced blood flow in the contralateral side due to a sympathetic reflex arising from the testicular artery under distress.
- Anomalies of testicular circulation are six times more frequent in men who have had orchiopexy for testicular maldescend compared with normal men. Although some of this may be intrinsic some of this vascular damage is iatrogenic.