

*In the name of God*

# The role of infections in male infertility

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About **15%** of the male infertility cases are linked to male genital tract infections.

Potentially correctable causes of male infertility.

# Deterioration of spermatogenesis and sperm function

- Spermatogenesis
- multiple mechanisms
- plasma membrane
- sperm DNA fragmentation

# SEMINAL LEUKOCYTES

Epididymis; role is controversially; ROS production

The general presence of leukocytes in semen does not correlate with sperm concentration, motile sperm count and normal sperm morphology .

Several studies show various techniques of assisted reproduction, namely IUI, IVF, ICSI and IMSI, and the leukocyte count does not have an influence on fertilization, implantation, pregnancy and live birth rates.

If leukocytes contaminated the washed sperm preparations, sperm functionality was significantly compromised.

It only appears that seminal leukocyte counts higher than  $10^6/\text{ml}$  lead to lower pregnancy outcome with an elevated rate of early pregnancy loss.

# SEMINAL LEUKOCYTES

These studies indicate that seminal leukocytes are only detrimental to spermatozoa and the fertilization process if they are in close vicinity of the male germ cells and if the seminal antioxidant system is not **overwhelmed** by the respiratory burst of activated leukocytes leading to the release of high amounts of ROS and cytokines.

If leukocytes are removed by suitable sperm separation techniques prior to assisted reproduction, the yielded spermatozoa are fully functional and competent to fertilize oocytes.

# Prostatitis

Prostatitis is an inflammation of the prostate gland with a prevalence between 4% and 11%.

Prostatitis is the most common urological diagnosis in younger and middle-aged men

Approximately 5%–10% of the diagnosed prostatitis are of bacterial origin .

While the Gram-negative bacterium *Escherichia coli* is the cause of bacterial prostatitis in about 80% of the cases other bacterial infections that have been isolated in prostatitis cases are Gram-positive enterococci *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Nesisseria gonorrhoea*, and *Klebsiella* .

# Prostatitis

prostatitis is characterized by very diverse clinical symptoms such as acute bacterial infection or chronic pelvic pain syndrome (prostatitis syndrome) and is

recognized as **one cause of male infertility** with the clinical presentation varying from asymptomatic inflammation to severe urological symptoms.

prostatitis is linked with decreased prostatic excretory function and has negative impact on male fertility.

potential affecting sperm morphology as well as sperm motility.

Men with chronic prostatitis present an episodic and relapsing condition characterized by pelvic pain, irritative voiding symptoms and effects on sexual function .

# Epididymitis

Epididymitis is an inflammatory condition of the epididymis in males presenting with acute unilateral or bilateral swelling of the scrotum.

In young, sexually active men, the inflammation is caused in most cases by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, whereas *E. coli* is pre-dominantly found in older.

In the latter group of patients, a higher risk of urethral strictures, bladder neck obstruction or benign prostatic hyperplasia (BPH) has been reported .

# Epididymitis

In addition to the loss of sperm function, inflammatory obstruction of the epididymal duct has been considered as an underlying cause of persistent azoospermia or oligozoospermia .

Histopathological results of epididymitis are characterized by massive infiltration of neutrophils in the interstitial compartment and loss of adluminal compartment and thickened lamina propria in the seminiferous tubules.

The inflammation may spread to the corresponding testes as 'epididymo-orchitis' and has consistently been associated with **high rates of infertility in many clinical studies.**

In a report by Osegbe, many men with unilateral epididymo-orchitis had contralateral biopsies showing **bilateral** gonadal damage and also experienced **azoospermia** .

# Orchitis

Orchitis is an inflammatory lesion of the testes that can be caused by *Chlamydia trachomatis* and *Neisseria gonorrhoea*.

These pathogens are the particular cause of the disease in men younger than 35 years.

In contrast, in older men, *Escherichia coli* has been found to be the predominant.

The mumps virus affects the testicles as mumps orchitis in 20%–30% of the cases which may lead to infertility in up to 87% of the patients .

# Orchitis

Clinically, an orchitis is associated with a pre-dominantly leukocytic exudate in the seminiferous tubules resulting in tubular damage.

Affected seminiferous tubules show degeneration of the germinal epithelium and thickening of the lamina propria which may result in fibrosis of the tubules .

As a consequence of this infection, testicular atrophy with spermatogenic arrest can occur. In turn, this would then result in poor sperm quality with low sperm counts .

In about 15% of the cases of azoospermia, an orchitis is the cause of an intratesticular obstruction .

# Urethritis

Urethritis is an inflammation of the urethra caused by sexually transmitted pathogens such as *Chlamydia trachomatis*, *Mycoplasma* or *Neisseria gonorrhoea*.

Non-sexually transmitted uropathogens such as Enterobacteriaceae and staphylococci are also triggering urethritis with an incidence between 20% and 31% .

In addition, non-infectious urethritis can be caused by injuries, masturbation or certain medical treatments.

# Urethritis

Symptoms of urethritis in men typically include urethral discharge, penile itching or tingling, and dysuria .

In a prospective study by Osegbe, 45 men with gonococcal urethritis showed extensive seminiferous tubular necrosis and inflammatory cell infiltration.

After a 2-year follow-up period, 27% of the patients were found to have persistent azoospermia, and 33% had no significant improvement in sperm density.

# Pathogens causing urogenital infections

The most prevalent pathogens in the male reproductive tract  
Chlamydia trachomatis, Ureaplasma urealyticum, Neisseria  
gonorrhoea, Mycoplasma hominis, Mycoplasma genitalium or  
Escherichia coli.

Except for Escherichia coli, which is particularly responsible for  
epididymo-orchitis or prostatitis in 65%–80% of the cases the other  
listed uropathogens are sexually transmitted.

# *Chlamydia trachomatis*

According to the World Health Organization (2011), chlamydial infections are the **most common** sexually transmitted disease.

This infection is rather **asymptomatic** in about 50% of men and up to 80% in women, and even newborns are infected during delivery accounting for 25%–50% of conjunctivitis and 10%–20% of pneumonia in babies.

Elementary bodies of *Chlamydia trachomatis* in the connective tissue in the **testis** and in **Leydig cells**. Other organs of the male reproductive tract such as the **prostate, epididymis and seminal vesicles** were also positive for Chlamydia.

Other studies showed that Chlamydiae can **directly** damage spermatozoa leading to cell death, induction of apoptosis and protein alterations.

# *Chlamydia trachomatis*

This pathogen is the most important etiologic cause of non-gonococcal urethritis and acute epididymitis in men younger than 35 years .

Kokab et al. established a significant relationship between infections with *Chlamydia trachomatis* and increased **IL-8** levels as well as seminal **leukocyte** concentrations

The percentage of progressively **motil** spermatozoa decreased in patients with *Chlamydia trachomatis* infections.

Infection with these bacteria has significant detrimental effects, not only on sperm parameters in general, but also specifically on **DNA integrity** .

# Ureaplasma urealyticum

*Ureaplasma urealyticum* and *Ureaplasma parvum* are the most important pathogens of the *Ureaplasma* genus with andrological relevance.

*Ureaplasma urealyticum* is frequently found in the urethra of sexually active men and causes symptomatic and **asymptomatic non-gonococcal urethritis** in up to 25% of the cases as well as pelvic inflammatory disease or infertility .

Apart from causing higher seminal **viscosity** an infection with *Ureaplasma urealyticum* has also effects on the male germ cells by negatively affecting sperm **morphology** as well as **concentration, motility** and vitality.

*U. urealyticum* is also increasingly identified to cause adverse pregnancy outcomes and both *U. urealyticum* and *U. parvum* are implicated in **chorioamnionitis**.

# ***Mycoplasma hominis and Mycoplasma genitalium***

These bacteria lack a cell wall. Andrologically important mycoplasmas are *Mycoplasma hominis* and *Mycoplasma genitalium*, both of which are causing urogenital infections and have been recognised as a common sexually transmitted disease .

Both pathogens are reported to affect the onset of pregnancy as they can attach and penetrate the sperm plasma membrane .

Spermatozoa from samples tested positive for *Mycoplasma DNA* show a lower penetration rate into zona-free hamster oocytes as compared with shows that even an asymptomatic infection with *Mycoplasma hominis* significantly affects semen parameters including sperm count, motility, morphology, seminal ROS production and total antioxidant capacity. In contrast, the ejaculatory volume and pH were not negatively affected. After antibiotic treatment with **doxycycline**, all seminal parameters improved significantly.

# *Neisseria gonorrhoeae*

*Neisseria gonorrhoeae* is a Gram-negative diplococcus bacterium, which equally infects men and women at reproductive age, causing gonorrhoea and is manifesting with **urethritis, cervicitis and/or salpingitis** .

In men, it can also lead to **prostatitis, epididymo-orchitis and infertility** due to testicular damage or ductal obstruction .

The attachment of these bacteria to other cells including spermatozoa, where they may bind to an asialoglycoprotein receptor that binds lipopolysaccharides is mediated by pili as T1 gonococci to the cell membrane .

In addition, T4 gonococci may also directly attach to spermatozoa In turn, this will attract leukocytes to the infection site and consequently increase seminal ROS levels, thereby damaging the male germ cells.

Usually, the infection is symptomatic with severe dysuria and a purulent urethral discharge. Gonorrhoea is the second most frequently reported sexually transmitted disease

# Viruses

A number of viruses can infect all parts of the male genital tract and thereby negatively affect the male fertility potential.

Among these viruses are the **mumps** virus (orchitis), **human immunodeficiency virus-1** (orchitis and prostatitis), **Coxsackie** virus (epididymitis), **cytomegalovirus** (vesiculitis), **human papillomavirus** and **herpes simplex virus** (prostatitis).

Effects increasing seminal leukocyte by direct toxic effects on the cells or indirectly via local inflammatory or immunological reactions

Modes viral infections enter the male urogenital tract system: ascent through the urethra or hematogenously.

# Viruses

Blood–testis barrier, the pathogens can possibly survive for extended periods by escaping immunosurveillance if they penetrate into the seminiferous tubules .

This is an aspect that can be of particular importance for assisted reproduction as this requires appropriate andrological diagnosis and management of the patient as well as proper handling of semen samples by the embryologist, because **semen is a vector** to propagate viruses.

HIV viruses can bind to and penetrate into spermatozoa via a CD-4-independent receptor .

Since angiotensin-converting enzyme-2 is present on Leydig and Sertoli cells and the fact that SARS-CoV-2, the virus that causes COVID-19, utilises this enzyme as a receptor to enter

human cells, it is plausible that COVID-19 could affect testicular function and therefore male fertility.

# THE END

