REVIEW

Impact of Genital Infections on Fertility

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Received 21 December 2004; received in revised form 22 January 2005; accepted 26 January 2005

Abstract

Infertility is a major problem of modern medicine since it affects almost 15% of reproductive-age couples. Tubal factor cases consist of a major group among the infertile female population. Adhesions, tubal mocosal damage or tubal obstruction interfering with ovum transport may be secondary to pelvic infections and subsequently lead to tubal infertility. The infections most frequently diagnosed regarding the female infertility involve *Chlamydia trachomatis*, gonococcal infections and pelvic inflammatory disease with anaerobes and facultative anaerobs. Tuberculosis appears as another important cause of infertility especially in underdevelopped countries. All these infections may lead to serious sequelae including infertility, ectopic pregnancy, chronic pelvic pain, hydrosalpinx and tuboovarian abcess. Additionally male urogenital infections such as urethritis, prostatitis, orchitis and epididymitis seem to be potentially preventable causes of male infertility and further research is mandatory to evaluate the impact of those infections upon fertility. As a conclusion early recognition of both male and female urogenital infections, prompt institution of appropriate antibiotherapy and proper follow-up should be our goals to prevent long term complications.

Keywords: infertility, pelvic infections, tubal factor

Özet

Genital Enfeksiyonların Fertiliteye Etkileri

İnfertilite, üreme çağındaki çiftlerin yaklaşık %15'i gibi önemli bir kısmını etkilediğinden modern tıbbın majör bir sorunu olarak karşımıza çıkmaktadır. Tubal faktör olguları ise infertil kadın popülasyonunda önemli bir grubu oluşturur. Adezyonlar, tubal mukoza hasarı veya ovum transportunu engelleyen tubal obstrüksiyon pelvik enfeksiyonlara sekonder gelişebilir ve tubal infertiliteye yol açabilir. Kadın infertilitesi ile ilgili en sık tanı koyulan enfeksiyonlar *Chlamydia trachomatis*, gonokok enfeksiyonları ile anaerob ve fakültatif anaerob mikroorganizmaların yol açtığı pelvik inflamatuar hastalıktır. Tüberküloz ise özellikle gelişmemiş ülkelerde infertilitenin diğer önemli nedeni olarak gözlenmektedir. Tüm bu enfeksiyonlar infertilite, ektopik gebelik, kronik pelvik ağrı, hidrosalpenks ve tuboovaryen apse gibi ciddi sekellere yol açabilir. Ayrıca üretrit, prostatit, orşit ve epididimit gibi erkek ürogenital enfeksiyonları da erkek infertilitesinin potansiyel önlenebilir nedenlerindendir ve bu enfeksiyonların fertilite üzerindeki etkilerini değerlendirmek için daha fazla çalışmaya ihtiyaç duyulmaktadır. Sonuç olarak, erkek ve kadın ürogenital enfeksiyonlarının erken tanınması, uygun antibiyotik tedavisinin derhal başlatılması ve olguların düzenli takibi uzun vadeli komplikasyonları önlemeye yönelik amaçlarımız olmalıdır.

Anahtar sözcükler: infertilite, pelvik enfeksiyon, tubal faktör

Introduction

Infertility is defined as getting no pregnancy despite one year of unprotected sexual intercourse. Infertility appears to affect 10-15% of all couples in general population. The prevalence of male factor infertility is reported as 25-40% while female factor infertility is found to be 40-55% and both male and female factors consist of 10% of all the etiologic factors (1).

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Pelvic infections leading to adhesions, tubal mucosal damage or tubal occlusion mostly cause tubal factor that accounts for 30-40% of female infertility cases. Patient characteristics associated with tubal infertility such as history of sexually transmitted diseases, multiple sexual partners, early onset of sexual intercourse, low socioeconomic status, being unmarried, use of intrauterine device and septic abortion are demonstrated to be related with reproductive tract infections (2,3). *Chylamydia trachomatis, Neisseria gonorrhoeae, Mycobacterium tuberculosis*, endogenous anaerobs and facultative aerobs, viruses (e.g. HSV, CMV) or infrequently encountered agents such as schistosomes are a group of microorganisms that result in infectious complications involving tuboovarian abcess, hydrosalpinx,

chronic pelvic pain, tubal damage, extrauterine pregnancy and finally infertility (4).

Infections may lead to male infertility with a prevalance of 6.6%. Inflammatory reactions of male reproductive tract such as prostatitis, epididymitis, orchitis may lead to irreversible destruction especially if they occur before puberty. Sperm production and maturation processes may be affected adversely resulting in quantitive and qualitative spermiogram abnormalities (5). In spite of determining the objective data related with *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Chylamydia trachomatis* infections in infertile males, impacts of those infections on male fertility and treatment approaches still remain controversial (6).

Prevention of genital infections and their adverse consequences should be of high priority. Advances in tubal microsurgery and Assisted Reproductive Technologies (ART) offer new treatment options in infertile couples suffering from devastating consequences of reproductive tract infections (1). In spite of enabling women with organic pelvic disease such as tubal factor and endometriosis to achieve pregnancy, genital instrumentation during ART may additionally provoke pelvic inflammatory diseases in females especially with asymptomatic microbial colonization (7,8). Microbial growth on tip of the transfer catheter may be an additional source of contamination which is thought to be related with IVF outcomes (9).

In this study, we aimed to review impacts of reproductive tract infections on fertility and remind the gynecologists that early recognisition of the infection, timely organization of the appropriate therapy and proper follow-up should be our goals to avoid immediate or long term complications including infertility.

Female Factors

Tubal abnormalities as a result of fallopian tube destruction or obstruction related with previous pelvic inflammatory disease (PID), previous tubal or pelvic surgery and peritoneal factors such as peritubal and periovarian adhesions occurring secondary to PID, surgery or endometriosis account for 30-40% of the female infertility cases (10).

A randomized, prospective and normalized study about sexually transmitted diseases (STD) was performed by Rodriguez et al (11). Their study included 487 patients, 376 of whom were infertile and the remaining 111 were not and acted as the control group. 47.3% of these infertile patients presented at least one infection: 10.7% had *Chlamydia trachomatis* infection, whereas only 0.3% had gonococcal infection. None of the study cases were determined as Syphilis. 12.9% of the patients were found to have yeast belonging to Candida species, 5% bacterial vaginosis, 3.8% *Escherichia coli* and 0.3% *Klebsiella pneumoniae*. The isolation rates of *Ureoplasma ureolyticum* and *Mycoplasma hominis* were 23.5% and 4.8% respectively. They detected antibodies against Hepatitis B (any serological marker) in 7.8% of the cases. The presence of chlamydia and *U. ureolyticum* infections appeared to be related with infertility ($X^2=6.070$, $p<0.005$ and $X^2=8.782$, $p<0.005$, respectively). As a conclusion it seemed to be necessary to perform routine tests for screening *C. trachomatis*, *N. gonorrhoeae*, and *Mycoplasma hominis* among infertile patients.

Chlamydial Infections

Tubal factor infertility seems to be the only preventable type of infertility. *C. trachomatis* is found to be responsible for approximately 40-50% of PID and salphingitis cases, 25% of ectopic pregnancies, and 50% of tubal infertility (10).

Long term sequelae due to *C. trachomatis* are determined as salphingitis, endometritis, oophoritis and cervicitis. Consequently long term complications secondary to salphingitis are not infrequent. Infertility due to bilateral tubal occlusion (20%), peritubal adhesions and recurrent PID present a couple of these sequaela. Additionally ectopic pregnancy due to tubal damage (interference of ovum transport through the tube or entrapment of the ovum secondary to microscopic tubal damage) and chronic pelvic pain due to hydrosalpinx or adhesions surrounding the ovaries may be the other consequences of salphingitis (12).

Chlamydia trachomatis infects the columnar cells of fallopian tube but produces little damage in tubal tissue cultures since the host response is more important than the direct toxic effects of bacterial products in the pathogenesis. Infected epitelial cells secrete a number of proinflammatory cytokines which are chemotactic for neutrophils and mononuclear cells. Experimental inocculation of the fallopian tubes of lower primates with *C. trachomatis* has shown that repeated exposure to *C. trachomatis* leads to the greatest degree of tissue inflammation and damage suggesting that immunopathology also takes place in the pathogenesis (11). *Chlamydia trachomatis* deoxyribonucleic acid or antigens were detected at a high percentage in the biopsy tissues of the fimbrial and peritubal adhesions by in situ hybridization or immunoperoxidase stain suggesting a persistent infection in these women even after antibiotic treatment (13).

Immunopathogenesis of *C. trachomatis* infection is explained by a number of mechanisms. At the initial stage of infection, humoral immunity in the form of secretory IgA antibodies targeting the major outher membrane protein of the pathogen, appears to be the significant protective response and the determinant of whether infection develops or is cleared. Immune pathways switching from an initial rapid TH2 (T helper 2) to an equally rapid but manageable TH1 response, maintaining a cellular response at an effective moderate level until resolution and the cell-mediated response is down regulated by the action of IL 10. The timing of immune events is critical in this process. If it is too early chronic infection can set in, otherwise if it is too late significant inflammatory damage results. Poor cell-mediated immunity causes inadequate clearence of infection and leads to chronic stage infection. Too strong response (delayed type hypersensitivity) leads to tissue damage. TH1 cytokines serve a dominant role in protective immunity and TH2 cytokines are associated with immunopathology (14).

Most women with tubal infertility have had silent infections but no history of a symptomatic pelvic infection or acquisition of a sexually transmitted disease. The majority of these women have serologic evidence of exposure to *Chlamydia trachomatis*. Heat shock proteins (HSP) which are essential components of every living organism, bind to nascent proteins and facilitate their intracellular transport and correct assembly and folding. When *C. trachomatis* is in its persistent state, a stressful condition leads to upregulation in the synthesis of HSP60 while the production of other chlamydial components is down regulated. HSP60 is also immunogenic and induces a potent pro-inflammatory immune response.

Antibodies to CHSP10 were more prevalent in women with hydrosalpinx (46.8%) than in women with male factor infertility ($p<0.0001$, 6%) or tubal occlusion ($p=0.0009$, 15.5%). HSP60 antibodies were equally more prevalent in women with tubal occlusion. HSP60 was more prevalent in those women positive for CHSP10 ($p=0.02$) or *C. trachomatis* antibodies ($p=0.04$) than in women lacking these antibodies (12,14). Antibodies to the CHSP 10 were more prevalent in women with obstructed tubes plus hydrosalpinges (HSP10 expression is greater and prolonged in women with hydrosalpinges). Antibodies to HSP60 were strongly associated with tubal infertility but their prevalence did not depend on the presence or absence of a hydrosalpinx. Patients with tubal disease with or without hydrosalpinges were equally likely to have had an elevated prevalence of circulating IgG antibodies which shows that systemic immunity differs from local cervical immunity (15).

The human serologic response to chlamydial HSP10, HSP60 and major outher membrane protein (MOMP) was measured by immunosorbent assay in three different groups (uninfected group, acutely infected group and women with tubal factor infertility). Sera from women in the acutely infected group and tubal factor infertility groups both demonstrated HSP10 more frequently and at a higher overall level than sera from healthy uninfected controls. Moreover, the infertile women had significantly greater HSP10 seroreactivity than the acutely infected women, indicating a concomitant increase of HSP10 recognition in populations with increasing levels of disease severity. HSP60 reactivity showed a similar correlation in these populations, while MOMP reactivity peaked at the same level in both acutely infected and tubal factor infertility populations but did not increase with the disease severity. Test populations were standardized by level of reactivity to formalin-fixed *Chlamydia trachomatis* elementary bodies (EBs) to address whether these associations were reflections of increased overall chlamydial exposure rather than a property specific to HSP10. Associations between HSP10 seropositivity and tubal factor infertility were greater in the EB+ subgroup while associations among the EB– subgroup were diminished. When restricted to the EB+ subgroups, HSP60 and MOMP responses in the tubal factor infertility population did not increase significantly over the level of acutely infected group responses. Thus, among women with similar exposure to chlamydiae, the serologic response to HSP10 exhibited a stronger correlation with tubal factor infertility than did the response to HSP60 or MOMP. These findings support the hypothesis that the serological response to *C. trachomatis* heat shock proteins is associated with the severity of disease and identifies HSP10 as an antigen recognized in a significant proportion of women with tubal factor infertility (10,12,14,16).

Human endocervix is a part of the mucosal immune system and is distinct from systemic immunity. Cervical antichlamydial antibodies correlate better with the presence of an active infection than circulating antibodies do (17).

In a study in which 70 women with tubal infertility were enrolled, 35 (50%) were seropositive for *C. trachomatis* (2 were IgM, 33 were IgG) (13). Only HLA class 2 alleles found in 10% or more of participants were analysed. DQA*0102 was found less frequently among women with C.trachomatis associated tubal infertility. Alleles linked to DQA*0102 and decreased odds of *C. trachomatis* microimmunofluorescenence antibody in women with tubal infertility, alleles linked to DQA*0102 at the DRB1 and B5 loci (DRB1*1503 and DRB5*0101) were found less commonly among *C. trachomatis* associated infertility cases than among infertile women without microimmunofluorescence antibody to *C. trachomatis*.

HLA DR1 *1503 was detected in seven (20%) of *C. trachomatis* seronegative women, whereas it was absent in 35 *C. trachomatis* seropositive women . DRB5 *0101, an allele in linkage disequilibrium with DRB1 *1503, was also less commonly detected in *C. trachomatis* seropositive women (6% versus 26% in seronegative women). There is a negative correlation of DRB1*1503 and DRB5*0101 with *C. trachomatis* microimmunofluorescence antibodies in women with tubal infertility. HLA class 2 allele is associated with an innate or acquired immune response that reduces the risk of *C. trachomatis* infection and reduces the risk of *C. trachomatis* associated tubal scarring. Individuals with DRB1* 1503/ DRB5* 0101 may resist *C. trachomatis* disease and /or clear cervical infection without inflammatory pathology (13).

Gonorrhea

Gonorrhea is caused by a gram-negative diplococcus, *N. gonorrhoeae*. Human is the only natural host for this agent. The majority of these infections are asymptomatic and for this reason untreated infections can result in disseminated gonococcal disease and acute pelvic inflammatory disease (18). The standard diagnostic test is a culture (19). Gonococci attach to the surface of the secretory columnar cells of the endosalpinx. Gonococcal pilli and perhaps other surface proteins (protein 1 and Opa protein (protein 2) are important for this attachment. Gonococci are then taken into the secretory cells and perhaps located between the cells and extruded through the base of the cell into the submucosal connective tissue. Ciliary motion mediated by lipooligosaccharide ceases, and then ciliated cells are sloughed from the mucosa (20).

Pelvic Tuberculosis

Pelvic tuberculosis is primarily caused by either

Mycobacterium tuberculosis or *Mycobacterium bovis*. The fallopian tubes are the predominant sites of pelvic tuberculosis, but the bacilli also may spread to the endometrium. The diagnosis may be confirmed by histology, hysterosalpingography, culture or by direct visualization via laparoscopy (21). Tuberculous salpingitis can lead to infertility. Tuberculosis can cause endometritis leading to Asherman's syndrome so this should be considered as another possible cause of infertility (22).

Viruses

Viral sexually transmitted pathogens such as human immunodeficiency virus (HIV), type II herpes simplex virus (HSV Type II), hepatitis B virus (HBV), human papillloma virus (HPV) and cytomegalovirus (CMV) may lead to PID. However, neither HPV nor HSV has been directly linked to subfertility (23). Eggert-Kruse and colleagues evaluated a potential association of genital HSV infection with reduced cervical mucus quality and a cervical factor in involuntarily childless females (23). Increased viscosity of the cervical mucus has been found more frequently in HSV positive women, but cellularity and penetrability of cervical mucus have been shown not to be changed. They concluded that under optimal endocrine conditions, cervical HSV infection in asymptomatic women is not a significant cause of impaired quality and reduced penetrability of the cervical mucus. Drug therapy was successful in women with positive serology in menstrual blood and HLA class 1 antigen Cw3 was found to be increased with HSV infection (24).

Schistosomiasis

Rare causes of Asherman syndrome include infections of the endometrium such as schistosomiasis (25,26). Disease manifestations due to schistosomal infection are due to end stage of parasite in the host and its interaction with specific and nonspecific inflammatory and immune responses. Schistosomiasis should then be considered as a possible cause of infertility and Asherman syndrome in those parts of world where it is endemic (27,28).

Pelvic inflammatory disease

Ascending infection of endometrium, peritoneum and fallopian tubes by colonized microorganisms in endocervix is called as pelvic inflammatory disease and is a common cause of morbidity such as infertility. Recurrent gonorrheal epizodes increase the incidence of tubal damage (29). Westrom's laparoscopic studies demonstrated an incidence of tubal infertility of 12%, 23% and 54% after one, two and three epizodes of PID respectively (30). Consequences of salphingitis include fusiform swelling and erythema of the uterotubal junction, presence of fimbrial phimosis or frank distal tubal occlusion (hydrosalpinx), prefimbrial phimosis or fine fimbrial adhesions which may impede ovum pickup. Coinfection with *Chlamydia trachomatis* is also common. *Mycoplasma hominis* which is a potential pathogen in PID is infrequently recovered from tubal or peritoneal fluid cultures in women with PID. Tubal tissue cultures have shown decreased ciliary activity, but no cytopathic effect has yet been demonstrated. *Mycoplasma hominis* may be associated with bacterial vaginosis (31). *Ureoplasma ureolyticum* has been isolated from patients with acute salpingitis, from pelvic fluid and from tubo-ovarian abscesses less frequently than *Mycoplasma hominis*. Facultative and anaerobic bacteria are often isolated from fallopian tube and cul-de-sac cultures of women with PID. Those most often recovered agents are *Peptostreptococcus*, *Prevotella*, *Escherichia coli*, *Gardnerella vaginalis* and facultative streptococci. These organisms are commonly found in the lower genital tract, so whether they function initially as direct pathogens or whether they require the presence of an initiating organism such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis* remains controversial (32).

In the case of tuboovarian abcess (TOA), pregnancy rates following the disease process have been reported to range from 9.5% to 13.8% after conservative medical management, 3.7% to 16% after unilateral adnexal procedures with preoperative antibiotics and 10% to 15% after antibiotic therapy combined with colpotomy drainage (33). Further investigation is mandatory to determine the effects of newer antibiotics, laparoscopic drainage and unilateral adnexectomy on infertility in unilateral TOA patients.

Discussion

Infections are major preventable causes of infertility and many infertile women present serologic evidence of past infection. Subclinical PID is also diagnosed frequently among women with lower genital infections but additional prospective studies are necessary to determine the reproductive impact of these asymptomatic upper genital tract infections (34). The occurence of pelvic infections leading to PID and its sequelae should be prevented. Careful screening, as well as early and agressive treatment, may help prevent some of these complications. Efforts should be focused on detecting these infections such as cervicitis at an early stage. The suggestion regarding the screening for *C. trachomatis* to be an effective intervention in the prevention of PID is supported by Grade 2C evidence (level B recommendation). Only small numbers of women have been studied and the follow up periods are short. The risk of a woman developing PID following detection of lower tract infection with *C. trachomatis* still remains to be uncertain. According to Level B recommendation screening for chlamydia using culture is effective in preventing PID in short term. Further randomized controlled trials are required to assess the screening procedure using nucleic acid based tests for longer follow up periods (35).

La Verda and colleagues showed that HSP10 is an antigen recognized in a significant proportion of women with tubal factor infertility (16). The association of the immune response with HSP10 and the severity of genital tract disease, and the recent report about chlamydial OMP2 that is related with immunopathology suggest that proteins other than HSP60 may have a role in the development of chlamydial disease or may be used as immunologic markers of advanced disease. Further investigation is required to better define how the immune system recognizes and responds to HSP10 in protection and/or immunopathology and to determine whether HSP10

participates directly in the development of disease and whether anti-HSP10 serology can be used for the diagnosis of advanced chlamydial disease (16).

Since published data regarding the impact of viral genital infections on female fertility appear to be scarce, further investigations are required to make his controversial issue more clear.

Male factor infertility

The prevalence of infections in male factor infertility is 6.6% (36). Infections may cause complications regarding the production and maturation of sperm and these problems are the most frequent causes of male infertility. Sperms may be immature, abnormally shaped, or unable to move properly or normal sperm may be produced in abnormally low numbers (oligospermia) or seemingly not at all (azoospermia). Inflammatory reactions of the prostate (prostatitis), epididymis (epididymitis), and testicles (orchitis) may lead to irreversible damage on fertility if they occur before puberty (37-39).

Mycoplasma hominis and *Ureoplasma ureolyticum* (UU) have been recovered from the cervical mucus and semen of infertile couples. Since the effect of the presence of these organisms on fertility still remains unclear, the role of treating these infections in an infertile population also is controversial (40,41).

In one study, 60% of infertile men who were culture positive for ureoplasma and whose infection was subsequently cleared by antibiotic treatment impregnated their partners, on the other hand the rate was only 5% among men whose infection was not cleared (42). In contrast, a double–blind study of doxycycline treatment for mycoplasma infection failed to show an effect on conception rates (43).

The results of nuclear chromatin analysis in *in vitro*-infected sperm cells indicate that *U. ureolyticum* causes premature chromatin decondensation and damage to DNA integrity in both human and ram sperm cells in a dose and time dependent fashion. *U. ureolyticum* causes mitotic alteration, especially chromatid gaps and chromatid breaks, in cultures of lymphocytes (40).

When *Ureoplasma ureolyticum* attaches to the surface of sperm it increases the hydrokinetic resistance which slows down the sperm movement. UU may interfere with the sperm-ovum identification and fusion if UU attaches itself to the rear of the acrosome or the equatorial area of the sperm. UU infection causes sperm tail curling, head shrinkage, neck swelling, sperm agglutination and an increase in the percentage of abnormal form of sperm. H_2O_2 which is detrimental to sperm is an essential metabolite of UU. The phosphatase A and C in the UU membrane can decompose the lipid of sperm membrane and destroy its integrity. The apoptosis rate of the UU infection group was found to be significantly higher than that of the control group ($P<0.01$) (41). Etiologic factors of male infertility can be classified as testiculer (orchitis) and posttesticuler (obstructive epididymitis and accessory gland infections).

Orchitis

Orchitis is significantly less common than either prostatitis or epididymitis. The major route of infection is blood-borne dissemination. Viruses such as mumps, echovirus, lymphocytic choriomeningitis virus and group B arbovirus are clearly implicated as important pathogens. Orchitis develops in about 20% of cases who are infected with mumps. Two thirds of the orchitis is unilateral. Following the infection testis can return to its normal size and function or may be atrophic. Atrophy is due to both viruses' direct effects on the seminiferious tubules and ischemia which is formed by the edema and pressure in tunica albuginea. Semen analysis turns to normal in 2/3 of the unilaterally affected men, in 1/3 of the bilaterally infected men. Atrophy turns to normal after the acute disease in 1-6 months.

C. trachomatis is a common cause of urethritis and acute epididymitis in men <35 years of age. Elevated levels of IgA specific for *C. trachomatis* in semen can be observed in approximately 45-50% of men with symptomatic, nonbacterial prostatitis and leucospermia, compared with 23.5% of fertile men and 27% of men without any signs of infection (6). Ombelet and colleagues found higher frequency of chlamydia specific DNA in semen of the infertile group but this difference was not statistically significant (44). Sequelae in male due to *C. trachomatis*s are prostatitis, urethritis, epididymitis, orchitis, veziculitis. *C. trachomatis* is responsible for 50% of epididymitis in male. Factors playing role in male infertility are inflammation due to antibodies in serum and semen, antisperm antibodies in seminal plasma, lowered levels of zinc, fructose, carnytine, alfa glycozidase due to accessory gland infection, lowering of the fertilizing effect of the spermatozoa, elementary bodies in gamete.

Asymptomatic inflammatory prostatitis

Asymptomatic inflammatory prostatitis is a new classification that includes a category of patients who have diagnosable prostatitis but no genitourinary tract symptoms. On semen analysis, increased numbers of round cells may prompt a diagnosis of prostatitis. Other terms used in infertility literature include "prostaseminal vesiculitis", "leucocytospermia", "pyosemia". High sperm volumes usually reflect relatively long periods of abstinence or inflammation of the accessory glands. WHO views ejaculates with more than 5 million round cells per milliliter or more than 1 million leukocytes per milliliter as abnormal, however, the prognostic significance of leukocytes in semen is controversial (45).

The concentration of white blood cells (WBCs) in the first semen sample was significantly higher in patients with a history of gonorrhea than in patients without a history of gonorrhea ($p=.001$). Previous viral infections were not associated with the concentration of WBCs in semen ($p>0.05$). Serologic markers indicating a past *C. trachomatis* infection were not associated with the concentration of WBCs in semen ($p>0.05$). The sensitivity and specifity of leukocytospermia for detecting *M. hominis* and *U. ureolyticum* infections were found to be 93%-10% and 65%-40% respectively. The sensitivity and specificity of leukocytospermia for detecting *C. trachomatis* infection could not be calculated because of the low prevalence of this organism (45).

Sexually transmitted epididymitis

The most common type of epididymitis in young people is the sexually transmitted one. *C. trachomatis* and *N. gonorrheae* are the major pathogens in this population. Complications of this type of epididymitis include abscess formation, testicular infarction, chronic epididymitis, and infertility. Absence of fructose or high pH may be associated with ejaculatory tract obstruction or seminal vesicle dysfunction.

Normal values for semen analysis (According to World Health Organization):
-Volume: >2 ml
-Sperm concentration: >20 million/ml
-Motility: >50%
-Morphology: >30% normal forms

The impact of genitourinary infection on semen parameters and male infertility is controversial. The presence of leukocytes, in a concentration of >1 000 000/ml in the ejaculate, is often used for the determination of an infection of the male sex glands. However other studies found no correlation between leukocyte counts, semen quality and the presence of micro-organisms. *Ureoplasma ureolyticum* and *Chlamydia trachomatis* are the two most frequently studied microorganisms regarding the male infertility. The prevalence of *U. ureolyticum* is approximately 40% in subfertile men and 28% in fertile controls. This microorganism has often been associated with decreased sperm motility, poor sperm morphology and an increase in the percentage of coiled sperm tails and probably these organisms attach to the spermatozoa (44).

In a study, semen characteristics were evaluated in 189 HIV infected men who were requesting for ART. In HIV infected men ejaculate volumes were lower, mean total sperm counts were decreased, nonspermatic cell concentrations were significantly higher. There was no relationship between semen characteristics and the mode of infection. Total sperm count was not affected by the duration of the infection. The HIV infected men displayed significantly lower percentages of rapidly progressive sperm than the controls; conversely the percentages of slow progressive sperm were significantly higher in HIV infected men. There was no correlation between percentages of rapid or slow progressive sperm and nonsperm cell concentrations. There were no changes in semen pH, sperm concentration, total motility, vitality and morphology (46).

In a study which was made in Italy, 122 patients with bacterial male accessory gland infections were studied. According to ultrasound criteria, patients had prostatitis (n=52), prostatovesiculitis (n=32) or prostatovesiculoepididymitis (n=38). Each group was than divided into two subsets; while one received ofloxacin or doxycycline treatment the other received no medical treatment. Female patners were also treated. Bacteriologic cure was highest (92.5%) after the third antibiotic course in prostatitis, followed by prostatovesiculitis (70.4%) and the lowest in prostatovesiculoepidydimitis (52%). At 3 months after therapy discontinuation, some sperm parameters, seminal WBC concentration and reactive oxygen species generated were ameliorated in prostatitis and prostatovesiculitis, whereas no improvement occurred in patients with prostatovesiculoepididymitis, except for the percentage of coiled tails. Antibiotic treatment in prostatitis and prostatovesiculitis patients led to positive effects on sperm output and spontaneous pregnancy rate (40%) by removing microbial and/or WBC related reactive oxygen species. The persistent infertility, dyspermia and sperm derived reactive oxygen species overproduction in prostatovesiculoepididymitis may be asssociated with a significant percentage of antibiotic-independent re-infection and/or to low antioxidative epididymal properties, which persisted following antimicrobial treatment (47).

Male infertility and viral infections

The role of viral infections in the pathogenesis of male factor infertility still remains unclear in spite of a number of studies demonstrating affected sperm motility parameters by the presence of HPV in sperm cells. Certain HPV-specific genes are shown to be actively transcribed (48). Additional research regarding this subject revealed data that sperm motility seems to be affected by the presence of adenovirus in human semen (49). Herpes simplex virus is another infectious agent that plays a significant role in male infertility. Early detection by PCR can permit successful antiviral therapy to increase the possibility of fertility restoration and long term protection of sperm quality (50,51). Bezold and colleagues concluded that herpesviruses involving HSV type 1 and 2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Human Herpes virus type 6,7,8 can be detected in about 17% of semen specimens from men seeking fertility evaluation. Only presence of EBV was found to be associated with altered semen parameters. Further research should be performed to evalute the prevalance of infection and the effects of antiviral therapy on male fertility (52). Levy and colleagues aggreed with these findings that CMV is present in the semen of a group of infertile males although it does not seem to play an important role in infertility. However the risk of transmission and developmental anomalies in infected fetuses must be determined (53). As a conclusion viral infections are still considered to have an uncertain role in the pathogenesis of male infertility in many aspects requiring further investigation.

Conclusion

Leukocytospermia is of no diagnostic value in selecting patients with an actual bacterial or viral infection and colonization of the genital tract (54). Silent genital tract infection or colonization with *U. ureolyticum* and *M. hominis* is a frequent finding in infertile men. The quantification of WBCs in semen is of no diagnostic value in selecting patients with an active genital tract infection and therefore can not replace culture (45). The effect of *C. trachomatis* on male infertility is controversial; antibody existence and leukocytospermia do not alter seminal parameters, but the indirect affects can not be ruled out. Some serovars and specific antibodies can affect the seminal parameters.

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