Chapter 13

Infection and Infertility

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Abstract

Infection is a multifactorial process, which can be induced by a virus, bacterium, or parasite. It may cause many diseases, including obesity, cancer, and infertility. In this chapter, we focus our attention on the association of infection and fertility alteration. Numerous studies have suggested that genetic polymorphisms influencing infection are associated with infertility. So we also review the genetic influence on infection and risk of infertility.

Keywords: infection, infertility, virus, bacterium, parasite, polymorphism, genetics

1. Introduction

The search for source of infection and infertility has been an active area of study for many years. Because the source of infection is complex, we divided the source of infection into three groups: virus, such as mumps virus, hepatitis B virus, human papillomavirus, herpes simplex virus, and human immunodeficiency virus; bacteria, such as *Chlamydia trachomatis* and *Helicobacter pylori*; and parasite, such as *Toxoplasma gondii*. First, we review the association of these infections and infertility. Because genetic influence may play important roles in regulating the infection in fertility, we also discuss the genetic effects on infertility, mainly the gene polymorphisms influencing infection and infertility in the following sections.

2. Infection and fertility alteration

2.1. Mumps virus infection and fertility

Even though Hippocrates described mumps many years ago and its vaccine has been available for long time, the disease continues to spread in the world. Mumps, a disease of droplet contact,

is transmitted to the population via the respiratory tract. The viruses multiply in upper respiratory tract mucosa and are carried to the affinity organs, such as the inner ear, pancreas and mammary glands, testis, and ovaries. [1]

Mumps virus is an RNA virus, which causes inflammatory reactions. Infections of mumps virus cause a variable clinical symptom. At the very beginning of infection, the virus attacks the testes, destroying the testicular parenchyma and reducing androgen production. [2] Most commonly they lead to fever and parotitis, and about 30% of male adolescents with mumps will develop orchitis. [3] Because orchitis is the most common complication in men, the disease sometimes develops in adult patients.

Previous studies consisting of about 300 patients with mumps orchitis were carried out between 1951 and 1970. Following mumps orchitis, cytogenic deterioration, with regard to sperm morphology, is a long-lasting effect. Spermiogenesis was greatly disrupted in half of the patients. In many patients whose testes were not atrophied, poor fertility was found persistently. According to the observations, sperm morphology was the most influenced, of the characteristics that were studied, and sperm count might be the least affected. [4] In conclusion, mumps virus infection is a risk factor for male infertility.

2.2. Hepatitis B virus infection and infertility

Hepatitis B virus (HBV) is a double-stranded DNA virus, which is one of the most common viruses threatening health of human beings. [5] HBV infection has been a very serious public health problem worldwide, especially in Asia. HBV infection was found to be related to decreased instability of sperm chromosome, sperm function, [5] and impaired sperm viability and normal morphology. [6] Recent work has confirmed that sperm is possibly a vector for vertical transmission of HBV. [7] However, little is known about the influence of HBV infection on sperm functions, which is vital for the fertility of those HBV carriers.

In 1985, it was discovered that HBV DNA was in spermatozoa and proposed that HBV may be a cause of male infertility by damaging spermatozoa. [8] But the mechanisms of the HBV impacting on human sperm remain unclear. Therefore, the studies of the influences of viral proteins on sperm function and the explanation of the pathways involved are critically important for male reproduction. HBs is the main component of HBV envelope proteins, so its effects on sperm functions, such as motility, fertilizing ability of sperm, and the according pathways require full studies. [5] Other studies indicate that HBV infection induces adverse influence on sperm chromosomes. Fluorescence in situ hybridization technique can visualize HBV DNA sequences that integrate into sperm chromosomes. Consequently, HBV enters germ line of male and integrates into the genome. [8]

Results of some studies indicated that HBs were able to reduce the human sperm fertilizing ability by inducing loss of sperm mitochondrial membrane, which potentially leads to the decrease of sperm fertilizing ability. [9] With increased concentrations of HBs, sperm were found to lose mitochondrial membrane potential and have decreased sperm motility and sperm fertilizing ability was affected. However, the molecular mechanism of HB-induced reproduction dysfunction needs to be explored in the future.

HBV can be transmitted vertically to the offspring through the male germ line because HBV may do harm to sperm function. [8] Some observations concerning the viral infection indicate that woman carriers of HBV may have reduced fertility potential, but further work is needed to explore the field and understand the effect of chronic viral infection on the reproduction. [10] So more attention should be immediately paid to the patients with HBV infection in the aspect of reproductive health.

2.3. *Chlamydia trachomatis* infection and infertility

Chlamydia trachomatis is an intracellular bacterium and needs living cells to multiply. Its chromosome includes about 1 million base pairs. Identified serotypes of *C. trachomatis* are eighteen. This kind of bacterium's cell cycle is quite different from that of others. [11]

C. trachomatis infections are considered to be the most common sexually transmitted bacterial infections all over the world. [12] The infection cycle starts with the entry of an infectious particle into an epithelial cell. *Chlamydia* infections cause great medical, economic, and even social problems. To diagnose *C. trachomatis* infection, nucleic acid amplification tests are done. [13]

Many studies have studied the link between chlamydial infection and semen quality. Some *in vitro* and *in vivo* studies tried to study the relationship between chlamydial infection and markers in spermatozoa. The establishment of a causal relationship between chlamydia and male infertility would have important effects on public health. [12] However, *C. trachomatis* infections are more harmful to the reproductive health of women than to men.

C. trachomatis is one of the major causes of mucopurulent cervicitis, which leads to about three kinds of complications and pelvic inflammatory disease in female. [14] Chlamydial pelvic inflammatory disease (PID) is a significant preventable cause of infertility and bad pregnancy outcome. According to a study about chlamydial infection and women, significantly higher prevalences of IgA and IgG antibodies were found among individuals suffering from infertility. The results of polymerase chain reaction (PCR) testing indicated that the women with positive IgA and IgG antibodies might possibly have been infected with *C. trachomatis* before. However, this study had some limitations, such as many bias and small sample size. [15]

Consequently, additional studies are necessary to get more epidemiologic data about *C. trachomatis* infection and to formulate useful prevention and intervention actions such as health education among adolescents. When talking about the treatment of this infection, the use of azithromycin should be considered during pregnancy. Treatment of sex partners is vital for reducing the risk of re-test after treatment.

2.4. *Toxoplasma gondii* infection and infertility

Toxoplasma gondii is a very common protozoan parasite infecting warm-blooded animals, including both mice and humans. About one-third of the human population has been exposed to it. [16] Approximately 50% of the humans are infected and developed a disease named toxoplasmosis, which is one of the most common parasitic zoonoses throughout the world. In different regions within any country and among different population groups based on various social, cultural lifestyle, and environmental factors, the prevalence of *T. gondii* always varies. [17]

Some studies indicate that low socioeconomic status has contributed to *T. gondii* exposure. [18] Another risk factor of the exposure might be the consumption of raw fruits and vegetables that were contaminated with *T. gondii* oocysts. Globally, very limited amount of studies of the agricultural population about the prevalence of *T. gondii* infection are conducted by researchers. The goal of a study was to investigate the prevalence and possible risk factors of toxoplasmosis among female farmworkers in a region of Turkey. [17]

In adults, *T. gondii* does not cause serious diseases, but in women infected with *T.gondii*, life-threatening complications such as congenital disease or even abortion occurs in the developing fetus. [19] However, there were some relations between infection of *Toxoplasma* and the sperm quality in human population. Zhou et al. [20] found that *Toxoplasma* infection in infertile human couples was higher than that in fertile ones. It may be related to the antisperm antibodies that were higher in infected human couples. A recent research of *T. gondii* infection in men with sterility indicated that among the cases of man's sterility, some of them were serologically *Toxoplasma*-IgG, IgM, and CAg positive. It was concluded that *T. gondii* infection may influence men's fertility. [21] Lu et al. concluded that acute infection of *T. gondii* can cause male infertility, and Sun et al. [22] concluded that acute *T. gondii* infection can devastate the reproductive function of infected male mice experimentally. Researchers used rats to study the effect of toxoplasmosis on male reproduction and found that in the *Toxoplasma*-infected group, sperm motility was decreased significantly. However, in median sperm concentration, they did not find any significant difference in infected animals and controls. Results indicate that there is possibly a correlation between toxoplasmosis and disturbed reproduction in male rats. [23]

Furthermore, a large-scale experiment with greater amount of animals and generations will be required to study the significant effect statistically. [24] Based on current researches, control programs of *Toxoplasma* infection in many countries should be implemented. Faster and reliable diagnostic tests should also be developed for male and female. [17]

2.5. Human papillomavirus infection and infertility

It was estimated that the prevalence of human papillomavirus was at about 12% globally in 2012, [25, 26] despite licensure of HPV vaccines in over 50% of the countries. Recent data indicate that in the United States more than 10 million people are newly infected every year and 79 million people are currently affected. [27] Inconsistent vaccination rates may contribute to continuing prevalence of this virus. [28, 29] Furthermore, in 2010, the whole cost of preventing and treating HPV-associated disease was said to be $8.0 billion. [30] Consequently, more attention has to be paid to the HPV infection.

Over 100 HPV types could spread by skin-to-skin contact, including sex, oral sex, sexual intercourse, and other contacts, involving the skin surfaces and genitals. People are commonly susceptible to this virus distributing in the skin and mucous membranes. It has been estimated that more than 50% sexually active populations will acquire the HPV infection during their whole lifetime, [31] and the risk of infection increases with the lack of condom use, the number of sexual partners, and smoking. [32, 33] Majority of sexually active adults may possibly acquire HPV during their lifetime. Generally, with the increasing amount of lifetime sexual partners, the risk of developing illness caused by HPV increases. [30] The human papilloma-

virus is considered to be one of the most common sexually transmitted viruses affecting fertility.

HPV is a kind of pathogen that induces chronic infections without any specific symptoms. It is generally accepted that sexually transmitted viruses can cause some changes in infertility. According to a summary of findings, there are some effects of HPV on sperm parameters. For example, HPV infections can alter sperm motility. On the other hand, HPV may increase sperm DNA fragmentation and change semen pH. In general, studies indicate that HPV infection is a factor adversely affecting male fertility or even resulting in infertility.

The studies that report on the differences in sperm quality between uninfected and infected men are discordant. *In vitro* studies have demonstrated that after incubation with specific HR-HPV DNA, higher motility of normal spermatozoa was found. [34] Additionally, there have been quite different influences of seminal HPV infection on some sperm parameters; a few studies have demonstrated that in HPV-infected men, sperm motility decreased, but they do not provide significant information on which sperm parameter could indicate HPV infection.

However, there was no significant difference in sperm quality between HPV-infected men and the uninfected. A study suggests that the presence of HPV may not affect sperm quality. In another recent study, about 300 semen samples of male partners of couples treated by IVF were screened for the HR-HPV DNA infection. [34] Between infected and uninfected men, the HPV DNA infection did not differ significantly. That is to say, sperm quality does not be impaired by the presence of HPV.

It was interesting that HPV-infected couples with the help of assisted reproduction technique might have an increased risk of pregnancy loss compared with the controls, according to a study. [35] However, additional larger studies are necessary to demonstrate the findings before clinical application and support the possibility of reducing the risk of the infection by assisted reproductive technology (ART). [36] Surely, including HPV infection, there are a great amount of other factors that cause infertility. [37] Small sample sizes and limited range of HPV types tested may possibly explain the discrepancies. In conclusion, studies of diverse results will promote more discussions about the influences of HPV infection on infertility.

2.6. Herpes simplex virus (HSV) infection and infertility

The Herpesviridae family consists of over 200 species infecting birds, mammals, fish, and so on. [38] In accordance with the World Health Organization (WHO), about 90% of the Earth's population is infected by viruses of the Herpesviridae family. HSV can be categorized into two types: HSV-1 and HSV-2. Through direct contact with sites of viral shedding or with muco-cutaneous fluids carrying the virus, individuals can contract HSV-1. HSV-1, the most prevalent virus among herpes viruses, is transmitted through oral secretions or sores, causing ocular and oral manifestations. Diseases caused by the virus are pharyngitis, tonsillitis, and gingivostomatitis, causing inflammation of the pharynx and tonsils and swelling of the gums. [39] During sexual contact with people having a genital HSV-2 infection, someone can get HSV-2 infection. Additionally, HSV-2 may possibly enhance the risk of acquiring HIV. Generally, someone

infected with it does not know the infection is present in his/her body. When it induces symptoms, it is extremely painful.

Some studies have established the association between HSV infection and male infertility. By semen analysis, researchers compare mean sperm count and morphology of samples. Using real-time PCR method, researchers find a prevalence of HSV DNA in semen. [40] According to a study of 279 infertile women attending an *in vitro* fertilization and embryo transfer program, the positivity rate for HSV was about 6.30%. [41] In order to investigate the prevalence of HSV in the infertile men, a study used serologic testing and PCR to test semen and blood samples. The PCR results indicated that the prevalence of HSV in semen was about 12%. [39] However, more researches should be conducted to correctly compare infertile individuals with and without HSV.

HSV targets the reproductive system, and the infection among males and females leads to infertility problems, but the mechanism seems different in the two populations. As shown in transgenic mice and in some experiments, it seems to affect the semen in males. [42] Interestingly, there have been no specific semen parameter associated with the HSV infection so far. [43] In women, HSV infection is a risk factor for infertility. The causal relationship between the infection and infertility in males and females would be established through further researches.

2.7. *Helicobacter pylori* infection and infertility

Helicobacter pylori is a spiral-shaped, microaerophilic organism, a member of the genus *Helicobacter*, and infects humans, especially at the gastroduodenal tract level. [44] Its genome is as small as 1667 kb, its niche is restricted, and the genome expresses a small amount of metabolic events. However, due to specific virulence determinants, *H. pylori* has been able to establish an adaptive evolutionary machinery. [45]

H. pylori infection is not limited in the gastroduodenal tract; *H.pylori* infection causes other digestive illness too. In the 1990s, some epidemiological studies indicated that *H. pylori* infection might be related to extra-digestive diseases affecting the heart and the blood vessels; then further studies showed that the disorders associated with this infection also affect the oropharynx, skin, and various other systems, such as the respiratory, endocrine, immune, hemopoietic, and central nervous systems. [46, 47]

Recently, more and more evidence in the literature indicates that *H. pylori* infection seems to negatively influence the reproductive function. Moretti et al. first investigated the association of *H. pylori* infection and female infertility. They reported an increased prevalence of *H. pylori* infection in female patients with fertility disorders compared to controls. [48] Several years later, a Japanese retrospective survey including almost 200 female patients supported the observation. [49] Figura et al. reported that the anti–*H. pylori* antibody levels in serum samples were higher in individuals with reproductive disorders than in controls and suggested that the risk of infertility may be increased by *H. pylori* infection. [48] Furthermore, Moretti et al. [50] found that the prevalence of *H. pylori* infection was higher in male patients with fertility problems than in controls.

Through various mechanisms, such as the release of molecular mimicry, inflammatory mediators, and systemic immune response, *H. pylori* infection can directly or indirectly impair reproductive functions. [51] Before considering reproductive disorders as another manifestation of extra-digestive diseases related to *H. pylori* infection, it is significant to carry out further studies about the prevalence of *H. pylori* infection in patients and controls, and particularly to perform study evaluating reproductive potential after *H. pylori* infection. [50] Furthermore, biologic researches to explain the relationship between *H. pylori* infection and infertility are required.

2.8. Bacterial semen infection and infertility

Almost 15% of cases of male infertility can be explained by infections about genitourinary tract. [52] Both infections and inflammation in the male reproductive system may impair the sperm cell, function, and the overall spermatogenetic process, [53 – 55] altering qualitative and quantitative sperm.

The bacteria, viruses, and fungi that contribute to semen infection may be sexually transmitted or come from the urinary tract; their effect on impairing male fertility has already been discussed. [56]

The sperm bacterial contamination is very normal and might contribute to the impairment of semen quality in infertile patients. Some studies have investigated the effect of bacterial semen infection in male fertility, but the putative influence of bacteria on semen quality is still inconsistent. [57]

Bacteria can affect the male reproductive function directly, by reducing the acrosome reaction, causing the agglutination of motile sperm, and changing cell morphology, and indirectly, by producing reactive oxygen species caused by the inflammatory response to bacterial infection. [58] The negative effect of bacteria on sperm motility is known to all. [55, 59] The findings of Moretti et al. [60] show that in all groups except for in two, sperm motility was reduced significantly. Moretti et al. suggested that the existence of bacteria would possibly alter the sperm quality. In the positive group, the mean sperm concentration for bacteria was significantly less than that in controls, whereas the value was always considered normal for WHO. Findings reported by other researchers [53, 57] indicate that *Escherichia coli*, *Enterococcus faecalis*, and *Ureaplasma* urealyticum have negative influence on semen quality of infertile patients. Alterations frequently observed in spermatozoa attributed to bacteria in both *in vitro* and *in vivo* conditions are reduced sperm concentration, sperm morphological alterations, loss of motility, and impaired acrosome reactions.

However, there is no absolute agreement on the detrimental effect of bacteria in the semen. A research reported that the bacteria isolated from the genitourinary tracts of men do not have any influence on semen quality; however, bacteria always impaired the antioxidant ability of sperm in infertile patients with pathological semen parameters. [55]

The exact molecular mechanism that the male fertility is affected by bacteria infection is not only multifactorial but also complex, and it is still a puzzle. [60] More studies based on the molecular approach should be applied to this problem to provide new explanation to the

microorganisms contacting with sperm and eventually monitoring the health of male genitourinary organs. In fact, re-evaluating sperm characteristics of patients treated would help to confirm the role of bacterial presence of the observed sperm abnormalities.

2.9. Human immunodeficiency virus infection and infertility

Initially, in the 1980s, human immunodeficiency virus (HIV) was found in the mononuclear cell fraction of the semen of one HIV-1-seropositive man and two men developing acquired immunodeficiency syndrome. [61] In the early period of the epidemic, those individuals diagnosed as HIV positive were not estimated to live a long life. [62] Since the HIV and AIDS were identified, in the management and long-term prognosis for infected people, vital advances have been made.

According to the WHO, about 75 million people have been infected with the HIV and more than 30 million humans have died of it. During the past 20 years, it has been extensively researched on the field of HIV infection, which invades the human immune system. In Sub-Saharan Africa remaining severely influenced, about 1 in 20 adults is infected by HIV and the number accounts for 71% of the infected people globally. [63]

With the appearance and especially the development of the immunodeficiency syndrome pandemic, attention of the sexual transmission of viruses in human population and its health effects has peaked accordingly. [61] HIV that causes AIDS is the most enormously studied virus among the sexually transmitted viruses. Some studies assessed the influence of HIV infection on sperm parameters in HIV-positive men. Researchers analyzed the association between markers of HIV infection and characteristics of semen. For example, a significant correlation between sperm count and CD4 cell count was demonstrated. Compared with fertile men, HIV-positive men's semen volume, sperm motility, and total sperm count were impaired. Dulioust et al. [64] investigated almost 200 HIV-infected men free from AIDS symptoms on the semen characteristics. Standardized methodology was used to analyze the semen samples collected. However, they did not observe any relation between HIV infection and semen characteristics. In the study of HIV-infected men, the semen changes may be not remarkable enough to affect fecundity greatly. The perfect study design of larger patient size is a longitudinal cohort study, which describes semen parameters during the development of an HIV infection. [65]

Studies showed that fertility was lower in HIV-1–infected women than the controls in Sub-Saharan Africa. It was the first time to suggest that HIV/AIDS was related to the fertility defects. [66] Recently, more studies indicate that fertility rates in HIV-infected women have decreased in the United States. [67] Among HIV-1–infected women, subfertility may be explained by biological alterations in reproductive physiology. Based on a reproductive endocrinology, HIV-infected women are more likely to have amenorrhea and protracted anovulation compared to the uninfected women. [68, 69] Many studies have linked HIV infection with premature ovarian failure. Additionally, pregnancy-related problems will continue after conception. In several clinical studies, it is more common that HIV-infected women may have pregnancy loss. [66] The correlation between HIV infection and infertility is a significant area for further research and investigation. The observations of those studies demonstrate that access to

investigating infertility and treating HIV-positive individuals is very limited in many countries. Healthcare professionals who care for these patients must pay more attention to conduct effective strategies to change the situation. [62] Researchers should design more treatments to minimize the risk of HIV transmission and to better understand the influences HIV and its treatments have on reproductive competence and fertility. [66]

3. Genetics influence on infection and risk of infertility

About 7% of men from the general population are infertile and 11.3% of married women suffering from infertility. [70, 71] Genetic inheritance could influence risk of many diseases like infertility. Over the last two decades, the genes responsible for many rare reproductive disorders have been identified by genetic linkage mapping with multiple affected individuals. [72] In male infertility, a cause for infertility cannot be identified in almost half cases. Severe spermatogenesis impairment is likely a genetic condition in many male infertility cases. [73] In female infertility, genetic factors also contribute to risk of many diseases, such as uterine fibroids, endometriosis, and tubal damage. Common genetic variants in complex diseases are simpler to detect by population studies (case–control study). Genome-wide association study (GWAS) is a developed method to study the genetic variants in population-based studies. GWAS methods could provide a powerful approach for mapping disease gene. [74] Single nucleotide polymorphisms (SNP) array and next-generation sequencing (NGS) could provide critical new date on rare variants. More than 30 million SNPs that segregate in human population have been identified. Gene discoveries from GWAS may not provide results that translated immediately into the clinic. They are the starting point to understand disease biology and already provided novel insights into biological pathways and novel biomarkers. [74]

In previous part, we have reviewed the association of infection and infertility, since gene polymorphism could influence infertility and infection status could also been influenced by gene polymorphism; therefore, we summarize the literatures reporting genetics influence on infection and risk of infertility below, because male and female infertility have different causes and subgroups; here we discussed them in two aspects.

3.1. Gene polymorphism influence infection and risk of male infertility

Even though many articles have been reported the association of gene polymorphism with male infertility, the association between gene polymorphism influencing infection and male infertility is limited to only two reports. [75, 76] As we know, unique immune environment of the testis is very important for spermatogenesis. Cytokines play critical roles in the maintenance of immune environment of the testis. Members of the interleukin-1 (IL-1) family are pleiotropic cytokines involved in the regulation of junction dynamics during spermatogenesis and further increase on infection. Recently, the polymorphism of the human IL-1B gene (C + 3953T) has been reported to associate with male infertility in asthenozoospermic patients from an Indian population. [75] In that study, the author found that the genotype frequencies of the IL-1B Taq C/T polymorphism were significantly higher in asthenozoospermic patients

(OR=10.4; CI, 2.50–43.96). Meanwhile, the author also found the association of variable number tandem repeat (VNTR) polymorphism of the interleukin (IL)-1 receptor antagonist gene (ILRN) with male infertility before. [76] The study indicated that risk of IL1RN2 polymorphism with male infertility (OR=1.43; CI, 1.1546–1.7804). In these two articles, we can find that the polymorphisms of IL-1 were both studied in these articles. One reason might be that these two studies carried by one research group and another reason might be that IL-1 plays important roles in testicular microenvironment. However, the total numbers of male subjects recruited in these two studies were limited to 452–689. So, it may lack sufficient statistical data to show the real association. Besides, the males in these studies were all Indians; therefore, further confirmation of the association in other ethnic population are needed. In addition, interactions of gene–gene and gene–environment factors were not considered. Environmental exposure of some chemicals or habits and customs of subjects such as smoking or drinking could influence the association of gene polymorphism and infertility. [77, 78] So we have reason to believe that the infection status could also impact the association of polymorphism and risk of infertility. Subjects with the same polymorphisms but different infection status may have different risk of infertility. Similarly, subjects with the same infection status but different polymorphisms may also have different risks. Thus, more complete researches are needed to determine the association of genetic polymorphism influencing infection and risk of male infertility in different subgroups and different infection status.

The associations between gene polymorphism and male infertility have been relatively widely investigated. However, the associations of gene polymorphism influencing infection and risk of male infertility were rarely confirmed. This may be the reason that researchers often focus on the polymorphism of genes playing roles in spermatogenesis. Since infection could increase the risk of infertility, more gene polymorphisms influencing infection are needed to be confirmed to be associated with male infertility in the future.

3.2. Gene polymorphisms influence infection and risk of female infertility

Tubal factor infertility (TFI) is one of the most common female infertility, and chronic inflammation induced by *C. trachomatis* can lead to TFI. The immune response is linked to cytokine secretion pattern, which is influenced by the host genetic background. So the associations between polymorphism of cytokine and TFI have caused researchers' concern. The HLA systems control immune responses by representing antigenic epitopes to immune T cells. By analyzing HLA class II alleles (DQA1 and DQB1) and CHSP60-specific lymphoproliferative responses in TFI patients and healthy controls, Kinnunen et al. [79] found that DAQ1*0102 and DQB1*0602 alleles together with IL-10-1082AA genotype were more significantly frequently in the TFI patients. Cohen et al. [80] also found that HLA-DR1*1503 and DRB5*0101 alleles were more commonly in *C. trachomatis* microimmunofluorescence seronegative women with infertility, and these alleles may lead to an immunologically mediated mechanism of protection against *C. trachomatis* infection–induced TFI. In 2015, Jansen et al. [81] analyzed the association of HLA-A rs1655900: G>A and susceptibility of *C. trachomatis* infection in a STD cohort and found that the carriage of HLA-A rs1655900 has no effect on susceptibility but might be

protective to the development of late complications, especially tubal pathology could be relevant.

As one of the most important cytokines, the associations between IL polymorphisms and *C. trachomatis*–related female infertility also have been widely studied. To investigate the genetic basis of Chlamydia-associated infertility and various manifestations of tubal damage, Ohman et al. [82] studied polymorphisms in cytokine genes, including IL-10, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta1, and IL-6, by a case–control study. The results suggested that IL-10 AA genotype and the TNF-alpha A-allele could increase the risk of severe tubal damage in women with *C. trachomatis* –related TFI. Meanwhile, in an *in vitro* study, to study the relationship between IL-10 promoter polymorphism and cell-mediated immune response, the researcher analyzed lymphocyte proliferation and cytokine, including IL-10, IFN-gamma, TNF-alpha, IL-2, IL-4, and IL-5, in subjects with different IL-10 genotypes. Results indicated that impaired cell-mediated response to *C. trachomatis* is associated with IL-10 genotype in subjects with high IL-10–producing capacity. [83] Unlike mentioned in male infertility, IL-B and IL-1RN gene polymorphisms are not associated with *C. trachomatis* –related TFI. [84] A polymorphism of NALP3 (gene symbol CIAS1) has been associated with decreased IL-1 levels and increased occurrence of vaginal Candida infection. Witkin et al. [85] selected women undergoing *in vitro* fertilization and tested polymorphism in intron 2 of the gene coding for NALP3 from their DNA. Researcher concluded that the CIAS1 7 unit repeat polymorphism could increase the likelihood of mycoplasma infection–associated female infertility.

Mannose-binding lectin (MBL) could activate the complement, modifies inflammation, and is involved in apoptotic cell clearance. [86] To study the role of MBL in tubal damage and female fertility, in 2010, Laisk et al. [87] performed a case–control study and found that MBL2 low-producing genotypes were associated with an increased incidence of pathogens associated with genital tract infections, hyper-producing MBL2 genotype HYA/HYA and low-producing MBL2 genotypes were associated with susceptibility to TFI, high-producing genotype HYA/LYA has a protective effect. In 2011, Laisk et al. [88] also compared four polymorphisms in MBL2 by a case–control study and found that the low-producing MBL2 genotypes were associated with susceptibility to TFI. Besides, the low-producing genotypes showed association of early pregnancy loss in IVF treatment.

Besides the most studied genetic polymorphisms, major histocompatibility complex class I chain–related A (MICA) gene is a potential host genetic candidate for *C. trachomatis* infections. To study the effect of MICA on the susceptibility to *C. trachomatis* infection and its association with tubal pathology, researcher selected 214 infertile women and found that women with tubal infertility more often had antibodies to *C. trachomatis*. Results suggested that the MICA locus might modify host susceptibility to *C. trachomatis* infection. [89]

From the literatures mentioned above, we can see that most of them are mainly in the study of TFI induced by *C. trachomatis*, the reason may be that *C. trachomatis* is the most common bacterial cause of sexually transmitted infections. [90] The numbers of subjects recruited in above studies are also limited (from 113 [79] to 811 [81]), and most of them were below 300 subjects. The mechanism of the genetic polymorphism is also limited. Besides, the interactions

of these genetic polymorphisms were not carried in these studies. Thus, further study, including more detail mechanism and more subjects from different countries or race, is needed.

In conclusion, genetic inheritance influences the risk of many reproductive disorders; genetic polymorphism could also increase the risk of infertility. The studies demonstrating the polymorphisms influencing infection and infertility were relatively rare. To date, studies on reproductive and genetic inheritance have used relatively small samples. More and more cohorts have been established or in preparation, so further genetic maker studies in larger samples with detail phenotypes and clinical information should be considered into disease risk classification. Along with detail environment and gene information, gene–gene and gene–environment interactions also shall be added in further studies. Since GWAS method has been widely improved to study other diseases, we can carry out infection and infertility researches by GWAS, so more and more genetic polymorphisms influencing infection and risk of infertility can be found out in the future. The system researches can provide theoretical and experimental support for clinical diagnosis and treatment guide.

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