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Association between Urogenital Tract Infections and Female Infertility

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Abstract

Female infertility, a condition responsible for social, psychological and emotional repercussion, is caused by ample variety of reasons *viz*. anatomical, endocrinological, infections. Amongst these, infections of the urogenital tract are often convicted in reducing the probability of conception in females. A wide array of bacteria, viruses, protozoa and fungi are usually encountered in genital tract of infertile females and they can employ plethora of virulence factors to interfere with normal reproduction process. Hence, the present article aims to garner and reiterate the significance of several microorganisms and their pathogenic mechanisms in induction of infertility in females.

Introduction

Infertility, involuntary childlessness, is a perplexing condition encountered by man since the dawn of civilization. Earlier, it was considered as an incurable personal distress that was perceived as destiny, however, with advances in medical research the scenario has changed. Nowadays, infertility is visualized as a disease of reproductive tract, which, if diagnosed successfully, may be treatable in certain cases [1]. The occurrence of infertility is linked to both male and female factors; therefore, the common wisdom is that its profound negative experience is to be equally shared by both the partners. However, in this male dominant society, the impact is not symmetrical. The brunt of this crisis falls disproportionately on females [2]. Thus, female infertility calls for special attention of the research groups and the same have started to devote more concern to female infertility. The major factors that have been documented to be associated with poor reproductive outcome in females include anatomical, hormonal, environmental and infections [3]. These factors may act in isolation or under certain conditions; combination of these factors may act.

Out of these factors, infections of the urogenital tract are often convicted in cases of infertility in females. Microorganisms colonizing female genital tract can play an important role in determining several aspects of reproductive health and are capable of causing various gynecological complications [4]. The negative influence on reproduction by microorganisms can be by direct injury to the reproductive tract mucosa, generation of inflammatory responses of the host or indirectly by affecting the functions of organs of genital tract [5]. Hence, in the present review, we sum up the diverse spectrum of microbial agents that have been demonstrated to elicit dramatic potential negative effects on reproductive health of females.

Bacteria

Chlamydia trachomatis

C. trachomatis, a Gram -ve, intracellular, aerobic bacterium, tops the list of major sexually transmitted pathogens with an infection rate of 100 million cases per year, worldwide [6]. Though it is reported to infect both genders however, it has a greater impact on women. The infection is asymptomatic when in lower genital tract in most women, and it may go undiagnosed and untreated. However, the problem arises when *C. trachomatis* ascends to upper genital tract as the manifestations and ramifications associated with this ascension are far more devastating. There are a number of theories that have been put forward to explain the possible mechanisms of female infertility caused by *C. trachomatis*. Tubal pathology and tissue scarring appears to be the major pathway by which *C. trachomatis* interferes with female fertility [7]. The organism that is generally confined to lower genital tract is speculated to travel to upper genital tract through four different ways. Firstly, they can bind to spermatozoa and use them as a vehicle for transportation to upper genital tract. Secondly, hormonal variations during the menstrual cycle may alter the formation and characteristics of the mucus plug that is responsible for providing defense against microorganisms, possibly affecting ascension. Thirdly, hormone levels at menarche may also cause cervical ectopy, which in turn increases the area for adherence of bacteria. Fourthly, movement to upper genital tract is also increased by enhanced sub-endometrial contractions prior to ovulation [8]. During ascension, they can cause irreversible harm to the fallopian tubes and resulting in an important gynecological condition i.e. pelvic inflammatory disease, because of which is altered fertility outcome [9]. It can also infect the columnar epithelial cells of the endocervix leading to cervicitis.

Another important technique employed by *C. trachomatis* is evading the host immune defense. It is mediated by migration to the upper genital tract from cervix, and persisting intracellularly in the epithelial cells in non-replicative form. It can lie in this form for even about a period of 5 years. Further persistence of *C. trachomatis* is favored by the possession of antiapoptotic property such as inhibiton of caspase [10].

The formation of cross-reactive antibodies has also been reported to be involved in causing infertility [11]. The cHSP10 and cHSP57/60 are found to possess homology to human proteins. Therefore, antibodies formed against cHSP60 in serum and follicular fluid of females infected with *C. trachomatis* might cross-react with human counterpart [12]. Further, antibodies against chlamydial chsp10 that mimic hHSP10 (early pregnancy factor) may lead to abortion, thereby, contributing to infertility.

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Chlamydial Lipopolysaccharide (LPS) also exerts terrible effects on female infertility. LPS could lead to considerable alteration at both the genetic and the physiological level upon exposure to LPS even for short duration [13]. The LPS of *C. trachomatis* has also been shown to destroy ciliated cells in female genital tract [14]. The lethal effect of chlamydial LPS is documented to be of stronger magnitude as compared to LPS of non-sexually transmitted pathogens [15].

Neisseria gonorrhoeae

N. gonorrhoeae, a gram-negative non-motile diplococcus, is estimated to infect 62 million people annually [16]. It is the second most common cause of STI after *C. trachomatis* that causes severe reproductive morbidities. The primary site of infection by *N. gonorrhoeae* is cervix; however, in about 10-20% cases the bacterium may ascend to upper genital tract. Therefore, acute PID marked by salpingitis, endometritis, tubo-ovarian abscess may occur, which in turn, lead to scarring, ectopic pregnancy, and chronic pelvic pain and infertility [17].

Various epidemiological studies have reported that the pathogen's deteriorating effects on fallopian tube is the root cause of infertility. Initially, *N. gonorrhoeae* attaches to the outer side of the secretory columnar epithelial cells (non-ciliated) of the mucous membrane that lines the fallopian tube. This adherence is mediated by Pili and other proteins such as protein 1 (surface proteins) and protein 2 (opa protein) [9]. The attack on fallopian tube is not restricted to non-ciliated cell but it continues to adjacent ciliated cells as well, where, it causes sloughing off ciliated mucosal cells. This damage to ciliated cells deters fallopian tube to carry out its job to transport fertilized ova to uterine cavity [19]. This abolition of the ciliated cells or reduction and consequent cessation of ciliary activity can be attributed to two gonococcal components: lipopolysaccharides (LPS) and monomers of peptidoglycan. LPS has also been found to aggregate at the cilial tip and cause sloughing of the ciliated cells in human fallopian tube organ cultures [19]. Apoptosis of uninfected cells because of LPS has also been reported. Induction of proinflammatory cytokines by Neisseria is postulated as another method through which tubal damage occurs [20].

Besides tubal factor, molecular mimicry is also an important factor that contributes to genesis of infertility. A surface protein expressed by *N. gonorrhoeae* is reported to share sequence homology with human chorionic gonadotropin. Since, HCG plays an important role in early pregnancy, thus, competition between the two to bind to common receptor may be an augmented risk to abortion [21].

Treponema pallidum

T. pallidum, the bacterial agent of syphilis, is a sexually transmitted microorganism, which primarily spreads *via* sexual intercourse, blood transfusion or maternal-neonatal transmission [22]. Reproductive tract infection by *T. pallidum* in women cause obstruction of fallopian tube, which in turn poses a hindrance in the way of transport of egg and embryo [23]. The positive link between *T. pallidum* infection and endometritis has also been documented in various studies [24]. It was corroborated by the histopathological examination of decidualized endometrial tissues of a female with 11th week abortion, which showed the presence of numerous spirochetes morphologically similar to *T. pallidum*. Zhu et al. (2015), while diagnosing the cause of post coital bleeding in female, provided a plausible link between syphilis and cervicitis [25]. *T. pallidum* has also been implicated in failure of *in vitro* fertilization (IVF). The infection may also lead to reduction in fertilization and implantation rates [26].

Mycoplasma genitalium

M. genitalium, a facultative anaerobe, belonging to genus genital mycoplasmas, is increasingly perceived as causative agent of Sexually Transmitted Infections (STIs) [27]. The examination of the existing data has confirmed the association of *M. genitalium* with female genital tract disorders with two-fold rise in risk for cervicitis, unprompted abortion, pelvic inflammatory disease, adverse birth outcome [and fertility loss 28]. Sethi et al. (2012) have stated that in comparison to healthy women, cervical canal of patients suffering from genital inflammation (20% of cases) showed their frequent presence [29]. This might be contributing to infertility problems detected in patients with idiopathic infertility and their partners suffering from undiagnosed oligosymptomatic infection with *M. genitalium*.

Given that, *M. genitalium* can populate upper genital tract of females with PID, it is likely that it can spread to the fallopian tubes and may lead to damage there. The destruction of cilia in the organ culture of human fallopian tubes is also found to be associated with the occurrence of *M. genitalium* [30]. Furthermore, females with tubal factor infertility also showed the presence of antibodies against *M. genitalium* [31]. A link between IgG against the immunodominant adhesion protein (MgPa) of *M. genitalium* and tubal factor infertility in females was also established by Ljubin-Sternak and Mestrovic (2014) [32]. *M. genitalium* can also adhere to human spermatozoa and cause damaging structural alterations such as looping or curving of tails, which further results in considerable decrease in motility as well as development of intracellular inclusions. Such structural changes have been related to the impaired fertility in females.

The repertoire of virulence factors that contribute to *M. genitalium* pathogenesis are a) adhesins at the terminal tip organelle that facilitate adherence to host epithelial cells, b) intracellular localization, c) secretion of enzymes and d) antigenic variation for evading host immune response [29].

For colonizing and causing infection, microorganism must adhere to host cells first as adherence is the fundamental factor in pathogenicity. Mycoplasmas, being the surface parasites of mucus membrane cells, rarely invade tissues but adhere obstinately to the mucosal linings of respiratory or urogenital tract. However, *M. genitalium* has been found to infect primarily the urogenital tract, but *in vitro* adherence is not constrained to uroepithelial cells only. It also adheres to variety of other eukaryotic cells and particularly to epithelial cells of fallopian tubes in humans. Adhesins that mediate adherence have found to be huddled at the terminal tip of flask shaped polar cell. Alvarez et al. (2003) reported that in addition to adhesins, enzymes such as Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH) also plays role in adherence of *M. genitalium* to vaginal and cervical mucin in humans [33]. This indicates that GAPDH works as a ligand that binds to receptors mucin and fibronectin, especially in cervical and vaginal problems.

Besides, Lipid-Associated Membrane Proteins (LAMPs) of *M. genitalium* were also shown to have an imperative role in the

inflammatory reaction of genito-urinary tract. In spite of the fact that mycoplasmas secrete hydrogen peroxide and superoxide metabolites, a great part of tissue degeneration is associated to the host cell reactions. *M. genitalium* also induces the production of cytokines (mainly TNF-α, IL-1α, IL-1β, IL-6, IL-8 and IL-10) by interacting with different components of immune system (including lymphocytes, monocytes, macrophages). The stimulation and suppression of immune cells by mycoplasmas also play a noteworthy role in pathogenesis [31].

Mycoplasma hominis

M. hominis is a gram-negative intracellular pleomorphic filamentous bacterium that is often linked to vaginosis, cervicitis, endometritis, PID and ectopic pregnancy [32,34]. These bacteria along with gram-negative bacteria have also been implicated in cases of premature birth, abortion and neonatal morbidity [35]. Infertility linked with *M. hominis* is due to cessation of movement of cilia in the fallopian tube, which hinders transportation of spermatozoa and embryo [36].

Genotal ureaplasmas

Genital ureaplasmas comprise of *U. urealyticum* and *U. parvum*, which are normally present in lower urogenital tract of humans with higher detection rates in females. On the other hand, they have also been convicted in number of cases of infections such as nongonococcal urethritis, infertility, postpartum endometriosis, chorioamnionitis, spontaneous abortion, stillbirth, premature birth and perinatal morbidity and mortality [37]. Various studies have reported that frequency of occurrence of *genital ureaplasmas* is high in infertile couples than fertile couples [38].

U. urealyticum present in vagina and cervix can ascend to the upper genital tract resulting in inflammation, which in turn leads to scarring of the tender tissue, which adds to the etiology of reproductive system anomalies. These organisms can also attack the amniotic cavity, persist there for a number of weeks, and instigate a strong inflammatory reaction. These infections may be asymptomatic; however, they play an imperative role in chorioamnionitis [39]. Similarly, *U. parvum* can also asymptomatically inhabit the upper genital tract of women. The occurrence of *U. parvum* in otherwise sterile part of the female reproductive tract may initiate long-lasting inflammation that may be responsible for infertility. These microbes can also cause morphological alterations in the external genitalia due to infiltration by inflammatory cells and resulting in adverse pregnancy sequelae [40].

The pathomechanisms of urogenital tract infection and infertility by *Ureaplasma* sp. can be attributed to a number of virulence factors i.e. IgA protease, hemolytic activity, phospholipases A and C, and adherence to the host cells. Also, it has been observed that chronic presence of microbes on mucosal surfaces of lower urogenital tract induces immune response to their antigens resulting in inflammation as revealed by increased levels of proinflammatory cytokines [41].

Gardnerella vaginalis

G. vaginalis is a gram-variable coccobacillus that is present in lower amount in the human vagina of healthy women. Being a facultative anaerobe, it has the ability to bear the high redox potential of a healthy vaginal microbiome [42]. The major microbe replaces Lactobacillus during the cases of bacterial vaginosis. Nwaziri et al. (2009) have also indicated that *G. vaginalis* is worthy of consideration in pregnancy associated complications in rats [43].

The infection in reproductive tract is mediated by attachment to host receptors, release of host cell specific cytotoxic substances and formation of biofilm [44]. The initial adherence to epithelial cells is assisted by the release of a cholesterol-dependent cytolysin, vaginolysin, which binds to the CD59 molecule of the host [45]. The survival strategy of *G. vaginalis* in the vagina is based on its ability to produce biofilm. Biofilm formation is increased through the mucinase activity of sialidase enzyme. *In vitro* studies have also shown high tolerance of *G. vaginalis* against the lactic acid and hydrogen peroxide produced by lactobacilli when present in biofilms [46].

The major mechanism of infertility in case of *G. vaginalis* is speculated to be because of deciliation of fallopian tube as studied in fallopian tubes and bovine oviducts organ culture. The organism as a whole, piliated or not, leads to cessation of ciliary beating and damage to mucosa. Cell free supernatant caused the similar effect which points towards the presence of soluble toxin. The toxin, however, is not human tissue specific but is speculated to play a significant role in development of salpingitis [47].

Mobiluncus spp

Mobiluncus spp consisting of *M. curtisii* and *M. mulieris*, are also associated with gynaecological enigmas. These bacteria are well cited as a member of vaginosis-associated flora. The mechanism of fertility alteration by *Mobiluncus* spp. was proposed by Taylor-Robinson and Boustouller, (2011), who demonstrated that *Mobiluncus* produces a cytotoxin that leads to deciliation, bloating and dissolution of ciliated cells in fallopian tube [48]. The occurrence of *Mobiluncus* spp. is also linked to perturbation and abolition of normal vaginal flora [49]. Another gram-negative, obligate anaerobic bacterium that has been reported to be associated with infertility is *Bacteroides* sp [50]. These microbes secrete lipopolysaccharide, which causes damage to epithelial cells and demolition of ciliary activity in the fallopian tubes [49].

Fusobacterium

Fusobacterium, the anaerobic, rod shaped, gram-negative bacteria, have also been implicated in infertility. The most commonly isolated species of *Fusobacterium* from the lower reproductive tract are *Fusobacterium naviforme*, *Fusobacterium gonidiaformans* and *Fusobacterium nucleatum*. Amongst these, *F. nucleatum* is frequently associated with premature and stillbirths in pregnant mice. It was also recovered from the amniotic fluid, placenta, and chorioamnionic membranes of women that delivered prematurely. It has special attraction for the cell found in the decidua basalis, decidual stromal and interstitial trophoblastic tissue [51].

Escherichia coli

E. coli, a gram-negative, facultative anaerobic bacterium belonging to family *Enterobacteriaceae*, is commonly observed as constituent of normal gut flora. Apart from being a normal inhabitant, it has the notoriety of being associated with genitourinary tract infections [52]. Out of all the cases of infertility caused by urinary tract pathogens, *E. coli* constitutes 70% of the cases Anchana devi (2013). It is speculated that the mode of entry into urethra is cross contamination from

the bowel [53]. Further, *E. coli* is one of the major bacteria that is frequently isolated from bacterial vaginosis cases and endometriosis [54].

Effect of *E. coli* on ciliated cells was determined in an earlier study by Laufer et al. (1984), wherein they observed complete loss of cilia as an outcome of administration of *E. coli* in fallopian tubes of rabbit [55]. Probable mechanism of infertility by lipopolysaccharide (LPS), the cell wall component of *E. coli*, was postulated by Agrawal et al [56]. They reported that the presence of LPS seems to alter the levels of cytokine TNF-α, as well as, LH and FSH. This perturbation in immunological and hormonal factors could result in implantation failure or loss of early pregnancy.

A number of reports are available in literature, which highlighted the detrimental effect of *E. coli* on sperm parameters. This could be attributed to direct adhesion to male gamete or production of soluble factors. The adhesion is mediated by bacterial pili that attach to the plasma membrane of spermatozoa and result in agglutination of spermatozoa. It could also lead to acrosomal loss upon *in vitro* incubation. It has also been observed that *E. coli* could interfere with sperm-oocyte fusion, the possible explanation for which was that *E. coli* binds to sperm equatorial region, which is the position of fusion [57]. Intravaginal inoculation of sperm agglutinating *E. coli* has also resulted in infertility in mice as demonstrated by Kaur and Prabha [58].

Staphylococcus aureus

S. aureus, though a commensal, is one of the most successful human pathogens with ability to infect every environmental corner of the host. Data emerging from recent studies is providing a proof of evidence in support of the vaginal colonization of Staphylococcus and infertility. Momoh et al. (2012) showed a prevalence rate of 38.7% of *S. aureus* from high vaginal swab and endocervical swabs of infertile females [59]. Another survey reported *S. aureus* as the main vaginal pathogen (57.33%) among infertile females and is often linked to bacterial vaginosis [60]. Being asymptomatic, it is often disregarded. However, Kaur and Prabha (2012) have demonstrated infertility in female mice because of vaginal colonization with sperm impairing *S. aureus* [61]. Also, it is associated with development of endometritis, a risk factor to female infertility. It has also been demonstrated that cytokines released in the uterine milieu in response to *S. aureus* can impair implantation, and placenta vascularization, leading to recurrent miscarriage [62].

Pseudomonas aeruginosa

P. aeruginosa is a gram-negative, ubiquitous, rod shaped opportunistic pathogen that has emerged as an important cause of gram-negative infection, particularly in immunocompromised patients. The infection may virtually involve each and every part of the body, in particular the urogenital tract. In an earlier study, Kaur et al. (1986) have demonstrated the isolation of *P. aeruginosa* from cervices of infertile females [63]. It was also isolated from cervices of infertile women along with the major sexually transmitted organisms.

King et al. (2002), demonstrated development of PID as a consequence of colonization of intrauterine device with *P. aeruginosa*, the source of which was speculated to be sexual contact or contamination during the insertion of IUD [64]. Apart from these, *P. aeruginosa* has been found to significantly alter sperm parameters *viz.* total count, progressive motility as well as viability of spermatozoa and acrosome integrity. Its quorum sensing molecule, 3-oxododecanoyl-L-homoserine lactone, and a cytotoxin named Exotoxin A is also reported to induce detrimental effects on spermatozoa [65,66]. The potential of *P. aeruginosa* to cause impairment of structural and functional parameters of spermatozoa in vito and infertility in female mice, upon intravaginal colonization with the same, has also been demonstrated [67].

Miscellaneous bacteria

A diverse spectrum of bacterial species *viz. Enterococcus, Klebsiella, Proteus, c, Streptococcus* have also been isolated from reproductive organs of infertile women as reported in different epidemiological studies [53]. In spite of not producing any overt symptoms in a current infection, these microorganisms may interfere with equilibrium of the vaginal microflora, thereby interfering with the normal reproduction process. Also, these microorganisms have been reported to alter various sperm parameters *viz.* motility, viability, morphology, acrosome reaction etc. that are the determining factors of infertility. The role of *S. marcescens* to render the female mice infertile when intravaginally inoculated, has been demonstrated in our laboratory [68].

Fungi

Candida albicans

The major fungal pathogen that affects the urogenital system is *C. albicans*. This normal inhabitant of the female reproductive tract has the ability to cause diseases varying from gentle forms of vaginitis and cervicitis, to a more critical form i.e. Recurrent Vulvovaginal Candidiasis (RVVC), which may alter vaginal mucosa, which may affect reproduction process.

The presence of *C. albicans* in vagina may also impair sperm motility as various studies have shown the negative influence of *C. albicans* on sperm parameters. The cell free filtrates of *C. albicans* possess inhibitory activity on motility of human spermatozoa and deteriorated the ultrastructure of sperm. The major bio active agents in the filtrates were reported to be acidic proteinases, phosphatidases and other soluble virulence factors. Farnesol, the quorum sensing molecule, induces significant loss of progressive motility which coincided with multiple damages in spermatozoa due to apoptosis and necrosis. At sub lethal doses, it can also lead to early loss of acrosome and DNA fragmentation of spermatozoa [66].

Viruses

Herpes Simplex Virus (HSV)

HSV, most common virus in humans, is accountable for a wide spectrum of diseases including neonatal infections and genital herpes [69]. The presence of HSV-2 was found to be significantly higher in women with secondary infertility than in comparison to fertile group and various clinical manifestations have been reported to be associated with genital herpes infections such as miscarriage and/or complicated pregnancy, leading to reduced fertility [70]. It has also been linked to altered quality of cervical mucus and cervicitis [71].

Human Papilloma Viruses (HPV)

HPV, sexually transmitted virus, is often encountered as leading

cause of cancer. However, a positive correlation between the HPV infections and reproductive alterations cannot be neglected [72]. Alteration in tubal factors as a result of HPV infection has also been established as cause of infertility. The virus can lead to reduction of Lactobacillus sp., which in turn tends to cause cervical pathologies It can also cause miscarriages or premature rupture of membrane [73].

Human immunodeficiency virus

HIV, the causative agent of acquired immunodeficiency syndrome, can be identified in both vaginal and cervical secretions as cell-free or cell-associated form. Most of the infections caused by HIV-1 in the female reproductive tract are supposed to have come from the cervix [74]. Kushnir and Lewis (2011) indicated the association between declining fertility and HIV-1 infection wherein they reported that infertility in individuals infected with HIV is 25-40% higher in comparison uninfected controls [75]. The systemic illness, stress, weight loss, and drug use may also impair the rate of conception. HIV infected women, due to immunodeficiency, are at an increased risk for concomitant sexually transmitted disease, which can lead to tubal blockage. These secondary infections may cause infertility.

Human Herpes Virus (HHV)-6

There are number of reports that link the incidence of HHV-6A virus in altered fertility outcome. Marci et al. (2016) reported 43% of endometrial epithelial cells positive for HHV-6A DNA in females suffering from unexplained infertility, whereas, no control women harbored the virus [76]. Gervasi et al. (2012) demonstrated HHV-6 infection in amniotic fluid of a patient who showed premature delivery and showed maternal–fetal HHV-6 infection resulting in abortion [77].

Cytomegalovirus (CMV)

Human CMV lies in latent phase in individual's body that under conditions such as weakened immune response can become active and elicit its effect. Owing to its ability to form cytomegalic inclusion particles, it has been reported to be involved in chronic endometritis, spontaneous abortion, fetal anomalies etc [78]. It not only plays a considerable role in infertility, but it may also give rise to obstetric impediments.

Parasites

Trichomonas vaginalis

T. vaginalis, a flagellated protozoan and a common cause of sexually transmitted infection, is distributed throughout the world with high prevalence rates.. This organism asymptomatically inhabits the vagina of about 3.15% of females [79]. Different research groups have reported that two times higher incidence of tubal infertility in females who showed a history of trichomoniasis in comparison to females with no such history [80]. Cultures were positive for *T. vaginalis* in 14.58% of the infertile couple in comparison to 2.5% fertile ones. This significant difference underlines the implication of *T. vaginalis* in female infertility [81].

Infection of reproductive tract by *T. vaginalis* seems to affect fertility outcome in different ways. *T. vaginalis* has been associated with vaginosis, salpingitis, vaginitis, cervical neoplasia, endometritis and adnexiti [82]. It can also induce inflammatory response in genital mucosa thereby; increasing the chances of atypical pelvic inflammatory disease and microhemorrhages, and these complications can result in female infertility [83]. *T. vaginalis* has been associated with complications during pregnancy. It is linked to increased risk of premature rupture of the placental membranes, premature labor, preterm delivery, low birth weight infants, and it also has a tendency to induce postpartum maternal sepsis in pregnant women [84]. Intrauterine infection with the parasite might result in poor development of the endometrium that negatively affects assisted reproductive procedures. The interaction of *T. vaginalis* with vaginal and cervical epithelial cells activates an immunosuppressive response from monocytes, macrophages, and dendritic cells, thus, affecting the immunological synchronization needed for the successful implantation of embryo.

The presence of this microorganism in vagina can lead to reduction in levels of C3 and C4 complement elements and also increases the level of IgA in vaginal discharge and serum prolactin [85]. Infection of the vaginal and cervical canal by the parasite can prevent free sperm movement, which could be attributed to a) direct binding of *T. vaginalis* to the sperm, b) circular whirling movement of T. vaginalis interrupting the normal horizontal movement of sperm within the vagina, or c) contact-independent mechanisms brought by substances secreted by *T. vaginalis*, as suggested by majority of *in vitro* studies. Through different microscopic studies they revealed that there occurs an initial tropism, followed by close proximity and finally a tight adhesion between spermatozoa and *T. vaginalis*. The reduction in motility was accompanied by intense sperm agglutination. The parasites could also maintain the spermatozoa adhered to their cell surface followed by phagocytosis of male gamete. Wiwanitkit (2007) described that the pattern of movement of T vaginalis within the vagina is vertical zigzag a consequence of which is circular whirling. He observed that during interaction in vagina the whirling movement of parasite interrupts the normal motility of spermatozoa, which might pose an obstacle in fertilization process [86]. Contact free alterations of sperm parameters *viz*. motility, acrosomal status, hypo-osmotic swelling, and *in vitro* fertilization capacity by *T. vaginalis* was documented by Roh et al [87]. They indicated that the release of extracellular polymeric substance (EPS), the toxic metabolic products are responsible for the above said alterations.

A number of other bio active agents such as proteinases, phospholipases, acid phosphatase, and peroxidases have also been isolated from *T. vaginalis*. They might increase the pathogenity of the organism and are identified to be involved in cytotoxicity, hemolysis and cytoadherence [88]. *T. vaginalis* escapes host immunity by utilizing various adhesion proteins, cysteine proteases, and lipophosphoglycan molecules. It attaches to vaginal epithelial cells using its barbed tail expressing surface protein p270. It also secretes proteases and a cell-detaching factor, which leads to strong host inflammatory response a repercussion of which is local cytotoxic effects, genital tract damage and negative reproductive effects [89].

Along with, the synergism of *T. vaginalis* with other microbes present in vagina may lead to severe reproductive repercussions. *T. vaginalis* supports the action of *M. hominis*, by carrying the bacterium within the protozoon cell, and by allowing its active replication, thus protecting the bacterium from the immune response and the

influence of therapies, thereby, favoring the dissemination through the reproductive tract. The concurrent presence of Trichomonasvirus and *T. vaginalis* may allow the virus to infect *T. vaginalis*, which in turn causes alterations in genome organization, protein coding, and replication signals of *T. vaginalis*, thereby, increasing the risk of reappearance of infection and resistance to the treatment [90].

Toxoplasma gondii

T. gondii is a ubiquitous intracellular protozoan that is projected to infect one-third of the global human population leading to a wide spectrum of illness [91]. Numerous clinical studies have provided different indices for the presence of link between toxoplasmosis and infertility. Recently published data have shown a positive correlation between prevalence of T. gondii infection and infertility [92].

The clinical manifestions of T. gondii infection in pregnant females are diverse. Latent asymptomatic toxoplasmosis exerts undesirable impact on early development of embryos, thus, pregnant females have prolonged pregnancy with less developed foetuses [93]. The association of toxoplasmosis and miscarriage has also been an issue of deep concern. A positive impact of latent T. gondii infection on the risk of miscarriage has also been shown [94].

It has been suggested that chronic infection is more implicated in reproductive disorder, which can be due to presence of cysts of T. gondii in different organs, in particular brain [93]. Cytokines triggered secretion of Corticotropin-Releasing Factor (CRF) by hypothalamus that results in activation of HPA axis followed by suppression of HPG axis, which inhibits the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, a consequence of which is Follicle-Stimulating Hormone (FSH) insufficiency, Luteinizing Hormone (LH) insufficiency and ovarian atrophy [95]. The scientists speculated that a chain of reactions that follows the release of cytokines in answer to T. gondii is involved in reproductive failure.

Entamoeba histolytica

E. histolytica is an anaerobic protozoan that is present ubiquitously, which causes an ailment known as amoebiasis. Infection to man occurs by oral ingestion of contaminated food or water. *E. histolytica* has been speculated to play an indirect role in female infertility. Various studies link *E. histolytica* with inflammation of fallopian tubes, ulcerative vulvovaginitis, endometritis, tubo-ovarian abscess and genital ulcers, which might be responsible for development of infertility in women [96].

Trypanosoma cruzi

T. cruzi, kinetoplastid flagellate protozoan, is an enzootic parasite that is one of the chief factors leading to deaths in Latin America. Globally, it is estimated to infect around 2 million women in reproductive age [97]. In case of pregnant women, the incidence rate may be as high as 64.4%, with about 12% congenital transmission [98].

There is paucity of clinical research demonstrating the relation between T. cruzi and infertility in humans; however, there are studies, which established pivotal role of T. cruzi in mice infertility. It can lead to drastic reduction in fertility outcome of female mice along with causing fetal death [99]. It could also result in smaller gestation period, decrease in fecundity, and increased utero and neonatal mortality in infected mice. Infertility in mice infected with *T. cruzi* might be a consequence of defects that occurred before implantation [100]. The mechanisms by which *T. cruzi* exerts deleterious effects on fertility outcome not established at present; but some plausible explanations have been anticipated such as infection of endocrine glands, attack on placenta, overproduction of inflammatory cytokines (tumor necrosis factor-α) in the oviducts and/or uterine horns, and suppression of implantation and cell division. Moreover, parasite load can also alter fertility outcome [98,100].

Trypanosoma brucei

T. brucei is the etiological agent behind the vector-borne parasitic disease, human African trypanosomiasis that is putting lives of 70 million people at risk. This organism has also been held culpable for reproductive alterations such as infertility, menstrual disorder, loss of libido, and amenorrhea in females [101]. In addition, the infection with T. brucei has been linked with irregular estrous cycle, fetal death, abortion, stillbirth, and neonatal death (Ikede et al., 1988). The mechanism of infertility in case of T. brucei has been attributed to the damage to hypothalamic–pituitary-gonadal axis that results in damage to the reproduction cycle [102].

Leishmania

Leishmania is a genus belonging to trypanosomatid protozoa and is accountable for the *leishmaniasis*. It has been linked to infertility in females. Cutaneous and visceral l*eishmaniasis* can lead to formation of lesions in genital areas thereby affecting fertility [103]. Further, proinflammatory cytokines (TNF-α and IFN-γ), produced at elevated levels in response to *leishmaniasis*, have negative impact on pregnancy [104].

Conclusion

It can be summarized from this review article that female genital tract is open to microbial colonization. Microbes and their metabolic actions may interfere with normal reproduction process. Hence, proper screening and treatment for microbial infection may help in successfully tackling the declining birth rates and raising the probability of conception.

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