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REVIEW

Human parasitic protozoan infection to infertility: a systematic review

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Abstract Protozoan parasitic diseases are endemic in many countries worldwide, especially in developing countries, where infertility is a major burden. It has been reported that such infections may cause infertility through impairment in male and female reproductive systems. We searched Medline, PubMed, and Scopus databases and Google scholar to identify the potentially relevant studies on protozoan parasitic infections and their implications in human and animal model infertility. Literature described that some of the protozoan parasites such as *Trichomonas vaginalis* may cause deformities of the genital tract, cervical neoplasia, and tubal and atypical pelvic inflammations in women and also non-gonoccocal urethritis, asthenozoospermia, and teratozoospermia in men. *Toxopalasma gondii* could cause endometritis, impaired folliculogenesis, ovarian and uterine atrophy, adrenal hypertrophy, vasculitis, and cessation of estrus cycling in female and also decrease in semen quality, concentration, and motility in male. *Trypanosoma cruzi* inhibits cell division in embryos and impairs normal implantation and development of placenta. Decrease in gestation rate, infection of hormone-producing glands, parasite invasion of the placenta, and over-production of inflammatory cytokines in the oviducts and uterine horns are other possible mechanisms induced by *Trypanosoma cruzi* to infertility. *Plasmodium* spp. and *Trypanosoma brucei* spp. cause damage in pituitary gland, hormonal disorders, and decreased semen quality. *Entamoeba histolytica* infection leads to pelvic pain, salpingitis, tubo-ovarian abscess, and genital ulcers. Cutaneous and visceral leishmaniasis can induce genital lesion, testicular amyloidosis, inflammation of epididymis, prostatitis, and sperm abnormality in human and animals. In addition, some epidemiological studies have reported that rates of protozoan infections in infertile patients are higher than healthy controls. The current review indicates that protozoan parasitic infections may be an important cause of infertility. Given the widespread prevalence of parasitic protozoa diseases worldwide, we suggest further studies to better understanding of relationship between such infections and infertility.

Keywords Infertility · Protozoan parasites · Infections

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Introduction

The high rate of infertility, inability to conceive offspring, is one of the most important and underappreciated reproductive health problems in many countries. According to data from a comprehensive meta-analysis study by the World Health Organization (WHO) until 2010, almost 50 million couples suffered from infertility worldwide (Mascarenhas et al. 2012). The results of this study showed that 1.9 % of women aged between 20 and 44 suffered from primary infertility, inability of young women to have their first live birth, and 10.5 % of women who already had one child

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suffered from secondary infertility that is inability in the have another baby (Mascarenhas et al. 2012).

The main causes of female infertility are anovulation, tubal–peritoneal disorders, endometriosis, uterine abnormalities, alternation in sperm migration, poor quality of the cervical mucus or eggs, and advancing of female age (Evers 2002; Brugo-Olmedo et al. 2001; Adamson and Baker 2003). The major causes of male infertility are ejaculatory dysfunction, varicocele, and infection of the adnexa glands (Brugo-Olmedo et al. 2001). The most of male infertility cases are due to low sperm counts (a sperm count of $<20\times10^6$/mL, oligozoospermia), poor sperm motility (<50 % with progressive motility, asthenozoospermia), and abnormal sperm shape (<30 % with normal morphology, teratozoospermia) (Brugo-Olmedo et al. 2001; Wong et al. 2000; Irvine 1998).

Infertility and infections

Many microorganisms including bacteria, parasites, yeasts, and viruses seem to be involved in male and female reproductive failure in various ways. Thirty-five percent of women with an infertility problem suffered from tubo-ovarian dysfunction and post-inflammatory changes in the oviduct and surrounding peritoneum induced by infection diseases (Novy and Witkin 2008). Granulomatous salpingitis due to bacterial and parasitic infections is a rare cause of tubal occlusion (Steinkeler et al. 2009).

In addition, the roles of inflammation, seminal leukocytes, and cytokines induced by infections are very important to cause of male fertility (La Vignera et al. 2014). Infections can induce serious damage to the reproductive system of humans and animals including chronic inflammation in the cervix and endometrium, dysfunction in the reproductive tract secretions, decrease in sperm motility and deformity of them, structural disorders such as intrauterine synechiae, and induction of immune mediators that interfere with gamete or embryo physiology (Novy and Witkin 2008). It has been shown that infection-related causes play an important role on the incidence of infertility in developing countries (Ombelet 2011).

Protozoan parasites are microscopic, unicellular organisms that are a major health problem worldwide due to the high prevalence and incidence. Their clinical symptoms are strongly associated with the pathogenic effects and their location in host (in tissues, intestinal, or blood). The life cycle, route of transmission, and clinical symptoms of protozoan parasites are summarized in Table 1.

This report aims to provide a review of the relation between parasitic protozoan infections and infertility in both men and women and does not cover the effects and consequences of parasitic infections due to congenital transmission on pregnant women.

Method

Search strategy

We searched Medline, PubMed, and Scopus databases and Google scholar to identify the potentially relevant articles concerning the association between parasitic protozoan diseases and infertility published from 1980 until January 2015. The keywords used in the literature were the combinations of protozoa names and words associated with infertility such as *Toxoplasma gondii* and/plus infertility, *Toxoplasma gondii* and/plus sterility, and *Toxoplasma gondii* and/plus reproductive disorder. This procedure was carried out for other protozoan parasites, such as *Entamoeba* spp., *Giardia lamblia*, *Trichomonas vaginalis*, *Cryptosporidium* spp., *Plasmodium* spp., *Trypanosoma* spp., *Leishmania* spp., etc. For those protozoans that skin lesions caused by them can lead to infertility, the following search terms were used: cutaneous leishmaniasis/amoebiasis/acanthamebiasis and genital tract/disorder, etc.

Types of studies

Abstracts and full articles that were written in English and relevant to the topic were enrolled in this study. We excluded studies and reports with minimal importance on the topics. Finally, we assessed information of 56 full texts and four article abstracts (including three Chinese articles and one Turkish article that had English abstract) that were related with our searching topics.

Data collection

Predesigned data extraction forms were used to collect data. Two reviewers (M.N.S. and A.R.) independently read through all the papers selected for detailed evaluation. We tried to record the changes that were caused by protozoa in the animal and human reproductive system and were implicated in infertility.

Results

Trichomonas vaginalis

Trichomonas vaginalis is a flagellated protozoan parasite with a worldwide distribution. This organism inhabits the vagina in the female and the urethra, epididymis, and prostate gland in the male (Hezarjaribi et al. 2015). *T. vaginalis* is present in about 3.15 % of asymptomatic women attending the infertility clinics (Rein and Chapel 1975). Some studies have reported that tubal infertility is twice as high in women who reported a history of trichomoniasis compared with women with no such infection (Grodstein et al. 1993; Sherman et al. 1987).

Table 1 Life cycles, route of transmission, and clinical symptoms of protozoan parasites affecting infertility

Parasites	Disease	Definitive host	Intermediate host	Route of infection	Clinical symptoms
Trichomonas vaginalis	Trichomoniasis	Humans	None, do not live outside host	Sexual contact	Male: urethritis, prostatitis, epididymitis Female: vaginitis, vulvar and cervical lesions, frothy vaginal discharge, vulvo-vaginal itching, burning, or soreness, dyspareunia
Toxoplasma gondii	Toxoplasmosis	Cat	Humans, animals	Ingestion of tachyzoites or oocysts	Healthy people: 80-90 % of patients are asymptomatic, lymphadenopathy syndrome AIDS patients: encephalitis Congenital toxoplasmosis: hydrocephaly, microcephaly, mental retardation, seizures, visual defects.
Trypanosoma cruzi	Chagas disease	Human, animals	Reduviid bugs (family: Reduviidae)	Feces of reduviid bugs	Chronic chagasic cardiopathy, "mega" syndromes, ventricular arrhythmias, congestive heart failure
Trypanosoma brucei spp.	African trypanosomiasis or sleeping sickness	Human, animals	Tsetse fly (*Glossina* species)	Tsetse fly bite	Fever, lymphadenopathy, central nervous system involvement, consciousness, coma
Plasmodium spp.	Malaria	Human	Mosquito (*Anopheles* species)	*Anopheles* bite	Recurrent fever, shaking chills, sweats
Entamoeba histolytica	Amebiasis	Human	None, survive encysted in environment	Ingestion of viable cysts	Amoebic dysentery, colitis, liver abscess
Leishmania spp.	Leishmaniasis	Human, animals	Sandfly (*Phlebotomus*, *Lutzomiya* species	Sandfly bite	Visceral leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis

El-Shazly et al. found *T. vaginalis* in 14.58 % of infertile females compared with the control group (2.5 %) (El-Shazly et al. 2001).

Among women, trichomoniasis may play an important role in premature rupture of the placental membranes, premature labor, and low-birth-weight infants in pregnant women (Hardy et al. 1984; Minkoff et al. 1984). It is also associated with cervical neoplasia (Afzan and Suresh 2012; Yusof and Kumar 2012; Zhou et al. 2001) and atypical pelvic inflammatory disease (Jaiyeoba et al. 2011), and these complications can lead to female infertility. This parasite can decrease C3 and C4 (the complement elements) and increase the IgA level in vaginal discharge and serum prolactin (El-Sharkawy et al. 2000).

Among men, trichomoniasis has emerged as a cause of non-gonoccocal urethritis and as contributing to male factor infertility (Pellati et al. 2008; Soper 2004). El Seoud et al. found *T. vaginalis* in 28.8 % of male patients with urethral discharge and 8.2 % of these patients suffering from impotence and infertility (El Seoud et al. 1998). This organism increases the seminal fluid viscosity, semen agglutination, and percentage of particulate debris that can lead to a decrease in sperm quality and motility. Moreover, it is a cause of the changes in normal morphology of sperms (abnormal sperms), viability, and membrane integrity. Nevertheless, such complications may be resolved after treatment with one dose of metronidazole (Benchimol and De Souza 1995; Benchimol et al. 2008; Sherman et al. 1987; Tuttle et al. 1977). *T. vaginalis* is able to phagocytose sperm cells and its by-products rapidly killed sperms in vitro, and these effects in humans may contribute to the infertility in infected couples (Benchimol and De Souza 1995; Benchimol et al. 2008; Jarecki-Black et al. 1988).

Toxoplasma gondii

Toxoplasma gondii is an intracellular protozoan that infects 20–80 % of the world's population in different areas (Meerburg and Kijlstra 2009; Skariah et al. 2010). There are few clinical studies concerning the relationship between *T. gondii* infection and female infertility. Kankova and Flager state that latent asymptomatic toxoplasmosis had adverse effects on early development of embryos in mothers (Kankova and Flegr 2007). A number of recently published studies have shown that infection with chronic *T. gondii* in infertile women is significantly higher than in healthy women (Li et al. 2011; El-Tantawy et al. 2014). Zhou et al. have

reported that prevalence of chronic toxoplasmosis in infertile couples (34.83 %) was significantly higher than in fertile couples (12.11 %). In addition, their results showed that anti-sperm antibody was significantly higher in *T. gondii* infected than that in non-infected couples (Zhou et al. 2001).

Also, several studies on laboratory animals have shown that infection with *T. gondii* could be a cause of infertility in experimental animals. In female mice, chronic toxoplasmosis causes endometritis, ovarian dysfunction, impaired folliculogenesis, ovarian and uterine atrophy, decrease in reproductive organs' weight and reproductive performance, adrenal hypertrophy, vasculitis, cessation of estrus cycling, and reproductive failure in experimental mice (Stahl et al. 1994, 1995a, b). A possible description is that the peripherally released cytokines in response to *T. gondii* reach hypothalamus and then trigger the release of corticotropin-releasing factor (CRF), resulted in activation of HPA axis (characterized by adrenal hypertrophy), and subsequently suppress the HPG axis by inhibiting the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, leading directly to the pituitary gonadotropin [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)] insufficiency and ovarian atrophy (Stahl et al. 1995b). In male mice, acute toxoplasmosis can induce pathological changes in different reproductive organs such as testes, vas deferens epididymis, and prostate and thalamus. Moreover, acute toxoplasmosis can lead to adverse effects on reproductive function of experimentally infected male mice (Yang et al. 2005; Sun et al. 2008). Terpsidis et al. founded that the sperm motility and concentration were significantly decreased in male rats chronically infected with *T. gondii* compared to the controls (Terpsidis et al. 2009). Additionally, they found spermatozoa abnormalities (bent tail, loss of hook shape, head lost, double head, and cytoplasmic droplet) in infected group on days 30 and 40 after experimental infection (Terpsidis et al. 2009). Lopes et al. have reported that *T. gondii* infection can lead to focal mononuclear interstitial inflammatory infiltrate in the prostate and seminal vesicles and diffuse testicular degeneration in experimentally infected male sheep (Lopes et al. 2011).

It seems that in the toxoplamosis, chronic infection is more involved in infertility and reproductive disorder. It might be explained by settlement of tissue cysts of *T. gondii* in various organs, especially in brain.

Trypanosoma cruzi

Trypanosoma cruzi is the causative agent of human Chagas disease, an enzootic condition affecting 16–18 million people in Latin America countries. It is estimated that at least 2 million women in reproductive age are infected with *T. cruzi* in Latin America (Alkmim-Oliveira et al. 2013). The prevalence of Chagas disease in pregnant women in Latin America ranges between 4 and 64.4 %, and congenital transmission occurs in up to 12 % (average around 4–6 %) (Cencig et al. 2013; Romero et al. 2011).

The studies on human are rare, but several studies showed the potent role of *T. cruzi* in mice infertility. Mjihdi et al. state that the acute infection with the protozoa *T. cruzi* totally impaired reproduction of female mice by drastically reducing their fertility and inducing tremendous fetal death (Mjihdi et al. 2002). They described the following changes in infected mice compared with controls: lower gestation, reduce in fecundity, and high utero and neonatal mortality. Their results showed that about 80 % of infected mice were infertile, and in those that developed gestation, all embryos died (Mjihdi et al. 2002). In subsequent studies, this group demonstrated that the infertility of mice acutely infected with *T. cruzi* arises from a defect occurring after mating and before implantation (Boufker et al. 2006). In addition, *T. cruzi* infection does not affect the yield of primary oocytes, oocyte maturation, ovulation, fertilization, and first cleavage of the zygote (Cencig et al. 2013; Boufker et al. 2006). Schuster and Schaub have reported that acute *T. cruzi* infection is associated with anestrus in experimental mice (Schuster and Schaub 2001). The mechanisms through which *T. cruzi* infection has adverse effects on fertility are currently not known, but some possible mechanisms are suggested, e.g., infection of hormone-producing glands, parasite invasion of the placenta, overproduction of inflammatory cytokines (tumor necrosis factor-α) in the oviducts and/or uterine horns, and inhibition of implantation and cell division. Moreover, parasite burden and strains of *T. cruzi* might also influence the outcome of infection on fertility and reproduction disorders (Cencig et al. 2013; Boufker et al. 2006).

Trypanosoma brucei species

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease that occurs only in 36 sub-Saharan Africa countries. It is estimated that the number of annual actual new cases is 20,000, and the estimated population at risk is 70 million people.

Sterility or infertility, menstrual disorder, loss of libido, impotence, and amenorrhea have been reported in human during trypanosomosis infection (Bouteille and Buguet 2012). Clinical signs in infected men and male animals with *T. brucei* species include scrotal dermatitis, orchitis, periorchitis, thrombosis of the pampiniform plexus vessels, degeneration of the seminiferous tubules, and testicular degeneration. Also, females show irregular estrous cycle, fetal death, abortion, still birth, and neonatal death (Ikede et al. 1988).

It is well documented that trypanosomosis infection in human and animals caused specific damage in the hypothalamic–pituitary–gonadal axis that which can be a cause of serious defects in the spermatogenic cycle in males

Table 2 An overview of common protozoan infections' impacts on male and female infertility

Phylum/order/family	Species (common name)	Geographical distribution	Effects on male infertility	Effects on female infertility	References
Sarcomastigophora Trichomonadida Trichomonadidae	*Trichomonas vaginalis*	Worldwide	1: Decrease in sperm quality (abnormality in count, shape, and motility) 2: Increase in seminal fluid viscosity 3: Urethritis	1: Cervical neoplasia 2: Atypical pelvic inflammatory 3: Increase in serum prolactin 4: Killing of sperms 5: Premature rupture of the placental membranes	El-Sharkawy et al. (2000); Hardy et al. (1984); Minkoff et al. (1984); Afzan and Suresh (2012); Yusof and Kumar (2012); Zhou et al. (2001); Jaiyeoba et al. (2011); Pellati et al. (2008); Soper (2004); El Seoud et al. (1998); Sherman et al. (1987); Tuttle et al. (1977).
Apicomplexa Eucoccidiorida Sarcocystidae	*Toxoplasma gondii*	Worldwide	1: Decrease in sperm quality (abnormality in count, shape, and motility) 2: Impairment in the hypothalamic–pituitary axis 3: Impairment in hormones (testosterone, LH, FSH)	1: Endometritis and vasculitis 2: Ovarian dysfunction 3: Impaired in folliculogenesis 4: Cessation in estrus cycling 5: Impairment in the pituitary–ovarian axis	Stahl et al. (1994, 1995); Yang et al. (2005); Sun et al. (2008); Terpsidis et al. (2009).
Sarcomastigophora Kinetoplastida Trypanosomatidae	*Trypanosoma cruzi*	Central and South America	Unknown, probably hormonal changes or decrease in sperm quality due to parasite load	1: Inhibitions of implantation and cell division 2: Hormonal changes 3: Overproduction of inflammatory cytokines in the oviducts and uterine horns 4: Invasion to placenta	Mjihdi et al. (2002); Boufker et al. (2006); Cencig et al. (2013).
Sarcomastigophora Kinetoplastida Trypanosomatidae	*Trypanosoma brucei* spp.	Western, central, and eastern of Africa	1: Impairment in spermatogenic cycle due to damage in pituitary gland 2: Damage to reproductive organs	1: Impairment in estrus cycle due to damage in pituitary gland 2: Fetal death, abortion	Bouteille and Buguet (2012); Ikede et al. (1988); Batista et al. (2007); Morrison et al. (1981).
Apicomplexa Eucoccidiorida Plasmodiidae	*Plasmodium* spp.	Africa, Central and South America, Middle East, Central Asia	1: Decrease in sperm quality (abnormality in count, shape, and motility) 2: Hormonal changes (testosterone ↓, cortisol ↑)	Unknown, probably hormonal changes	Singer et al. (1987); Ezeh and Modebe (1996); Zei et al. (1990); Astolfi et al. (1999); Muehlenbein et al. (2005); Raji et al. (2006).
Sarcomastigophora Amoebida Endamoebidae	*Entamoeba histolytica*	Worldwide	1: Damage to reproductive organs	1: Salpingitis, ulcerative vulvovaginitis 2: Endometrial infection, tubo-ovarian abscess 3: Mimicking carcinoma of cervix	Calore et al. (2002); Citronberg and Semel (1995); Othman and Ismail (1993); Mhlanga et al. (1992); Niederhauser et al. (2007).
Sarcomastigophora Kinetoplastida Trypanosomatidae	*Leishmania* spp.	Africa, Middle East, Mediterranean region, Central and South America, parts of Asia	1: Decrease in sperm quality (abnormality in count, shape, and motility) 2: Genital lesion 3: Testicular amyloidosis, chronic prostatitis, epididymal inflammation	1: Unknown, probably genital lesion	Gülüm et al. (2012); Diniz et al. (2005); Mir et al. (2012); Schubach et al. (1998); Cabello et al. (2002); Kapila et al. (1994); Blickstein et al. (1993); Coto and Aguilar (1987).

and estrus cycle in females (Morrison et al. 1981; Batista et al. 2007; Ikede et al. 1988). The abovementioned content suggests that infection with *Trypanosoma brucei* spp. can be a cause of infertility in sub-Saharan Africa countries.

Plasmodium spp.

Malaria is a life-threatening mosquito-borne disease which affected millions of people around the world. Some of studies have shown that heat has an inhibitory effect on the male reproductive system (Thonneau et al. 1998; Rachootin and Olsen 1983). Therefore, complications of acute malaria such as fever may be disrupting human reproductive system. Singer et al. have reported that malaria infection decreases the semen quality and causes severe oligozoospermia, necrozoospermia, or azoospermia in men (Singer et al. 1987). The high fever during the acute stage of malaria may be a cause of oligozoospermia. In addition, some studies have shown that patients with genetic disorder such as sickle cell abnormality, thalassemia, and G6PD deficiency in high endemic areas for malaria have milder oligozoospermia, in either acute or past infection stage, and are more fertile than people with the normal genotype (Ezeh and Modebe 1996; Zei et al. 1990; Astolfi et al. 1999). An interesting explanation for these conditions could be greater immunity and resistant of these patients against malaria. Muehlenbein et al. have reported that testosterone levels are positively associated with parasitemia in adult human males infected with *Plasmodium vivax*, and infected males exhibit significantly lower testosterone levels and significantly higher cortisol levels compared with healthy controls (Muehlenbein et al. 2005).

Raji et al. showed that *Plasmodium berghei berghei* decreases motility, concentration, and viability in sperm of male infected mice. Also, there was a decrease in serum levels of testosterone and increased cortisol level in infected mice compared with the control group (Raji et al. 2006). The finding that acute malaria can impair semen quality and have an impact on sexual hormones is interesting and needs more investigations.

Table 3 Diagnostic methods and commonly used drugs for treatment of protozoan infections described in the male and female infertility

Protozoan infection	Parasitological methods for diagnosis	Serological and molecular methods for diagnosis	Commonly used drug
Trichomonas vaginalis	Wet-mount preparations, cultures, Papanicolaou smears, or special stains on samples taken from the posterior vaginal fornix or urethra.	Immunochromatographic assay, APTIMA *T. vaginalis* assay, BD ProbeTec *T. vaginalis* Qx Amplified DNA Assay, Affirm VPIII test.	5-Nitroimidazoles such as metronidazole or tinidazole
Toxoplasma gondii	Recognize of the parasite in stained tissue biopsy and cerebrospinal fluid (CSF), animal inoculation.	Immunofluorescent antibody test (IFA), indirect hemagglutination assay (IHA), enzyme-linked immunosorbent assay (ELISA), PCR, real-time PCR, nested PCR.	Pyrimethamine, sulfadiazine, clindamycin
Trypanosoma cruzi	Thick and thin blood smears, culture, xenodiagnosis technique, animal inoculation	ELISA, IFA, IHA, PCR, real-time PCR, nested PCR.	Benznidazole, nifurtimox, allopurinol
Trypanosoma brucei spp.	Microscopic examination of lymph node aspirate and blood and concentration techniques are needed such as quantitative buffy coat and microhematocrit centrifugation technique, animal inoculation	Card agglutination test (CATT), ELISA, IFA, IHA, PCR, real-time PCR, nested PCR.	Pentamidine, suramin, melarsoprol, eflornithine, and nifurtimox
Plasmodium spp.	Clinical diagnosis, microscopic examination of thick and thin blood smears	ELISA, IFA, IHA, PCR, real-time PCR, nested PCR.	Chloroquine, quinine, primaquine, proguanil, mefloquine, artemisinin, artesunate, fansidar.
Entamoeba histolytica	Stool examination and staining, culture, biopsy, sigmoidoscopy or colonoscopy.	Enzyme immunoassay (EIA), ELISA, IHA, latex agglutination, immunoelectrophoresis, counterimmunoelectrophoresis (CIE), PCR, real-time PCR, nested PCR.	Diloxanide furoate, paromomycin, iodoquinol, metronidazole, ornidazole
Leishmania spp.	Microscopic examination of skin sores for cutaneous leishmaniasis and bone marrow biopsies for visceral leishmaniasis, culture, animal inoculation	Direct agglutination test (DAT), Latex agglutination, ELISA, IFA. PCR, real-time PCR, nested PCR.	Pentavalent antimonials (Sb^V) such as Pentostam and sodium stibogluconate are drug of choice for all types of leishmaniasis; amphotericin B, paromomycin, miltefosine, pentamidine

Entamoeba histolytica

Entamoeba histolytica is an anaerobic parasitic protozoan that is found worldwide, especially in developing countries. It is responsible for a disease called amoebiasis, and transmission to man occurs by oral ingestion of contaminated food or water. *E. histolytica* may play a role in infertility indirectly. There are many case reports that *E. histolytica* can cause salpingitis (Calore et al. 2002), ulcerative vulvovaginitis (Citronberg and Semel 1995), endometrial infection (Othman and Ismail 1993), mimicking carcinoma of cervix (Mhlanga et al. 1992), tubo-ovarian abscess (Niederhauser et al. 2007), and genital ulcers that may be associated with infertility in women and men.

Leishmania spp.

Leishmania is a genus belonged to trypanosomatid protozoa and is the parasite responsible for the disease leishmaniasis. Cutaneous and visceral leishmaniasis can induce genital lesion in human and animals (Schubach et al. 1998; Cabello et al. 2002; Kapila et al. 1994; Blickstein et al. 1993; Coto and Aguilar 1987). A non-healing hyperkeratotic plate on the penis is reported due to the cutaneous leishmaniasis (Gülüm et al. 2012). Testicular amyloidosis, degeneration, progressive atrophy, and azoospermia were observed in experimentally infected hamster with *Leishmania donovani* (Gonzalez et al. 1983), and inflammation was observed in the epididymes, glans penis, and prepuce of dogs with visceral leishmaniasis (Diniz et al. 2005). Additionally, some studies showed that infection with *Leishmania* spp. induced infertility, chronic prostatitis, hematospermia, epididymal inflammation, alteration in seminal compounds, and sperm abnormalities such as poor motility, detached heads, and tail defects (Mir et al. 2012; Assis et al. 2010). Moreover, proinflammatory cytokines such as TNF-α and interferon-γ, produced at high levels in response to leishmaniasis, have adverse effect on outcome of pregnancy (Krishnan et al. 1996). An overview of common protozoan infections' impacts on male and female infertility is presented in Table 2.

The authors did not observe any evidence for impact of other protozoan parasites on infertility in search results. The mechanism of protozoan infections causing infertility and reproductive disorders is unclear and needed more investigations. Nevertheless, our search results in the literature suggest several reasons for impact of protozoan infections on the human and laboratory animal reproductive system, such as the following: decrease in semen quality, lesions and deformities of the genital tract, hormonal disorders, the harmful effects of produced proinflammatory cytokines, inhibition of cell division in embryos, invasion of utero-placental unit, and fetal death.

According to our review, a reason for high rate of infertility in developing countries may be high levels of infection including protozoan parasitic infections. It is possible that early diagnosis and treatment reduces complications of these parasites. The gold standard for diagnosis of protozoan parasites is identification of the causative parasite in suspect specimen. Moreover, history and clinical manifestations are useful. Diagnosis is usually based on microscopy, serological, and molecular methods. Treatment of these parasitic diseases is complex, and treatment options for different protozoa differ. In addition, drug resistance is reported worldwide. In Table 3, we summarized some of the parasitological and serological methods for the diagnosis of protozoan infection and commonly used drugs for treatment of these infections.

Conclusion

Many factors are involved in male and female infertility. Infection diseases are one of the most important causes of infertility in either both sexes. Little attention is paid to the effects of parasitic infection on infertility. Protozoan parasitic infections may be an important risk factor to infertility, although the importance of these parasites is not clearly understood. Therefore, further investigations should be performed to study the causal relationships between protozoan infections and infertility.

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Compliance with ethical standards

Conflict of interest The authors have nothing to declare.

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