J Gynecol Obstet Hum Reprod xxx (2017) xxx–xxx

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Review

An updated literature review on maternal-fetal and reproductive disorders of *Toxoplasma gondii* infection

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ARTICLE INFO

Article history:
Received 27 September 2017
Received in revised form 1st December 2017
Accepted 4 December 2017
Available online xxx

Keywords:
Toxoplasma gondii infection
Reproductive health
Abortion
Infertility

ABSTRACT

Background. – *Toxoplasma gondii* infection is one of the most prevalent infectious disease with worldwide distribution. Congenital toxoplasmosis is annually responsible for 1.20 million disability-adjusted life years around the world, but often it is overlooked many countries.
Methods. – We performed an updated review to summarize the current researches on fetal, neonatal and maternal consequences of *T. gondii* infection and also adverse effects of toxoplasmosis on women reproductive organs.
Results. – *T. gondii* infection could be cause of several abnormalities from hydrocephalus, microcephaly, deafness, abortion and still birth in fetal to psychomotor retardation, intellectual disability, hearing loss, slower postnatal motor development during the first year of life; and chorioretinitis, cryptogenic epilepsy and autism spectrum disorders in newborns. Moreover, this infection is related with neuropsychiatric disorders such as anxiety, schizophrenia spectrum disorders, depression, decreased weight, autoimmune thyroid diseases, self-directed violence, violent suicide attempts in mothers. This literature review emphasized that toxoplasmosis could be an important neglected factor endometritis, ovarian dysfunction, impaired folliculogenesis, ovarian and uterine atrophy, decrease in reproductive organs weight and reproductive performance in women. We reviewed role of the immunological profile such as pro-infiammatory cytokines and hormonal changes as main potential mechanisms related to this infection and development of maternal-fetal and reproductive disorders.
Conclusion. – *T. gondii* is associated with several brain related disorders in both mothers and newborns, and also it is cause of several abnormalities in reproductive organs. Early diagnosis and treatment of the infection could be effective to significantly improve the clinical outcome.

Introduction

Infectious diseases in pregnancy include TORCH complex (toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, Rubella, Cytomegalovirus, Herpes infections, hepatitis infections and human immunodefciency virus) and other such as listeriosis, malaria and ZIKA virus are responsible several adverse maternal and fetal outcomes [1,2].

Toxoplasma gondii is an obligate intracellular protozoan that causes a worldwide distributed zoonotic disease known as toxoplasmosis [3]. *T. gondii* infects most genera of warm-blooded animals including humans. It is generally assumed that approximately one third of people around the world be chronically infected with *T. gondii* [4]. The prevalence of toxoplasmosis is different between countries from lowest seroprevalence (1%) found in some countries in the Far East to the highest (90%) in some parts of European and South American countries [4]. The main pathways for *T. gondii* infection among humans are eating of raw or undercooked meat containing *T. gondii* tissue cysts, ingesting sporulated oocysts from soil, water, unwashed vegetables or contaminated hands, and acquiring congenital infection through the placenta [5–7].

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https://doi.org/10.1016/j.jogoh.2017.12.003
2468-7847/

Table 1
Prevalence of *Toxoplasma* infection among pregnant women in different countries in last six years.

Country	Year	Method	Sample size	Overall prevalence (acute infection) %	Ref.
Japan	2011	Latex agglutination	4466	10.3% (0.25)	[21]
Ethiopia	2011	ELISA	201	83.6% (1.4)	[22]
Taiwan	2012	ELISA, IgG avidity	1783	9.3% (0.0)	[23]
Egypt	2012	ELISA	323	67.5% (2.8)	[24]
Iran	2012	ELISA	555	41% (1.4)	[25]
Turkey	2013	IgG avidity	4651	39.9% (88)	[26]
Brazil	2014	ELISA, IgG avidity	487	68.3% (5)	[27]
Thailand	2014	ELISA, IgG avidity	760	25% (0.0)	[28]
Poland	2014	ELISA	8281	40.6% (ND)	[29]
Democratic Republic of Congo	2014	ELFA	781	80.3% (4.4)	[30]
Norway	2015	ELISA	1922	9.3% (ND)	[31]
Mexico	2016	ELISA, IgG avidity	338	6.5% (0.2)	[32]
Italy	2016	ELISA	36,876	ND (0.192)	[33]
Saudi Arabia	2016	ELISA	326	21.2% (1.2)	[34]

ND: not determined; ELISA: enzyme-linked immunosorbent assay; ELFA: enzyme-linked fluorescent immunoassay.

Although infection of healthy individuals is mild and frequently self-limited, the neurotropic complications of toxoplasmosis such as encephalitis, brain abscess and sometimes death are manifested when it is reactivated in immunocompromised patients [6]. Congenital *T. gondii* infection can lead to abortion or several abnormalities such ocular and neurological impairment [8]. In addition to above-mentioned manifestation, several recent studies performed in human and animal model have demonstrated that latent or acute toxoplasmosis is associated with reproductive organs disorders, infertility, sperm abnormalities, behavioral changes and neurological disorders in pregnant women and other people [9–18].

Although many epidemiological and casual evidences suggest that toxoplasmosis is an important disease in reproductive medicine, but it is often overlooked in obstetrics and gynecology or reproductive health clinics and is considered as a neglected tropical disease. In this paper we briefly reviewed maternal, fetal and neonatal consequences of *T. gondii* infection and also reviewed routine strategies for diagnosis and treatment of infection.

Congenital toxoplasmosis

Congenital infection occurs often when pregnant women become infected during gestation, and preconception infection confers little or no risk to the fetus [19]. Furthermore, vertical transmission could be occurred throughout reactivation of infection in immunocompromised pregnant women with previous latent toxoplasmosis [20,21]. The rate of transplacental transmission and the severity of fetal damage depend on gestational age and applying, or not, of prenatal anti-parasitic treatment [8]. Transmission rate of tachyzoites, one of the infective forms of *T. gondii* that can be colonized in placental tissues, during the first and second trimesters of pregnancy is less than 10% to 30% respectively, and increases to nearly 90% during the last weeks of third trimesters [8,22]. The placenta plays an important role in trans-placental transmission, as it is a natural barrier to protection of the fetus against infectious agents and also a target tissue for parasite multiplication [8,23]. In fact, the placental barrier is more efficient to inhibit the tachyzoites transmission at the beginning of gestation, but becomes more permeable at the end of pregnancy [24].

It is estimated that global incidence and burden of disability-adjusted life years (DALYs) related with congenital toxoplasmosis be 190 100 cases (95% credible interval, CI: 179 300–206 300) and 1.20 million DALYs (95% CI: 0.76–1.90), annually [25]. High burdens were seen in South America and in some Middle Eastern and low-income countries low burdens were seen in some European countries. The prevalence of toxoplasmosis among pregnant women in different countries [26–39] is presented in Table 1.

The consequences of *Toxoplasma* infection during pregnancy for fetal and neonatal

Transplacental transmission *Toxoplasma* tachyzoites during embryogenesis can result to very bad consequences for fetal development and often leading to widely abnormalities from hydrocephalus, microcephaly, deafness, and psychomotor retardation to abortion and still-birth [8,40–44]. It is observed in a study by ultrasound scan that development of fetuses at week 16 of pregnancy in women with latent toxoplasmosis is lower than healthy controls [45]. Ocular manifestations are also more severe when infection is acquired in first trimesters; these complications include increased intraocular pressure, microphthalmia, strabismus, optic neuritis, cataract, and retinal necrosis that can result to blindness [8,40,46–49].

It seemed that immunological profile against *T. gondii* plays a significant role to induce of these manifestations. Whereas interleukin-10 (IL-10) and other cytokines related with T helper-2 (Th-2) are main immune response in the placental microenvironment [50], Th1-associated immune profiles are responsible for host resistance to *T. gondii* infection, which secrete interferon-γ (IFN-γ), pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [51,52]. Shiono et al. have demonstrated that IFN-γ synthesized following *T. gondii* infection can led to abortion in pregnant wild type mice [53]. Hackmon et al. reported also that IFN- γ is involved in preeclampsia in pregnant women [54]. Moreover, inflammation and parasite multiplication can result to destruction of the white substance and block the aqueduct of Sylvius in the fetal brain tissue, resulting brain abnormalities such as hydrocephaly, microcephaly and psychomotor retardation [8].

Fetal infection at the second trimester resulting to milder complications include, splenomegaly, hepatomegaly, cerebral calcifications, pneumonitis, anemia, epilepsy, thrombocytopenia-induced petechiae, rash, and retinochoroiditis [48,55–57]. When maternal infection occurs during the third trimester the most of neonates (more than 80%) are asymptomatic, however retinochoroiditis and neurologic deficits in childhood or early adulthood might be developed, if these newborns not treated appropriately in early age [40–59,60,61]. Moreover, some retrospective or prospective cohort studies have reported that the risk of schizophrenia and related psychoses and also intellectual disability, hearing loss, slower postnatal motor development during the first year of life, chorioretinitis during the ages of 20–30, cryptogenic epilepsy, autism spectrum disorders, Down syndrome, Alzheimer's

Please cite this article in press as: Fallahi S, et al. An updated literature review on maternal-fetal and reproductive disorders of *Toxoplasma gondii* infection. J Gynecol Obstet Hum Reprod (2017), https://doi.org/10.1016/j.jogoh.2017.12.003