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CONGENITAL TOXOPLASMOSIS: AN OVERVIEW ON TRANSMISSION, DIAGNOSIS AND TREATMENT WITH REFERENCE TO EGYPT

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Abstract

Congenital toxoplasmosis is a zoonotic protozoan infection caused by the intracellular coccidian (phylum Apicomplexa) *Toxoplasma gondii* (*T. gondii*), which has a worldwide distribution. All warm-blooded animals are susceptible to infection and about 30% of the world's population is affected. The organism is transmitted transplacentally; following initial maternal infection, vertical transmission occurs from an infected pregnant mother to her fetus, mostly in the third trimester of pregnancy. The severity of fetal infection is determined by the pregnancy stage and whether the infected mother had received an efficient treatment in the early gestational period or not.

A better prognosis is expected for children whose mothers were treated with anti-*Toxoplasma* medications. Some factors favor infection transmission and progress of congenital toxoplasmosis as the parasite genotype, the immune status of the mother and the fetal or neonatal ability to develop an immune response against *Toxoplasma*. Possible outcomes of fetal infection include abortion, intrauterine growth retardation, jaundice, hepatosplenomegaly or intrauterine fetal death. Nervous system complications like intracranial calcifications or hydrocephalus as well as retinochoroiditis are all possible consequences. Commonly, there are no specific symptoms at birth and complications may appear at an older age. Congenital toxoplasmosis is treated by spiramycin in pregnant women, while, drugs were used during late gestation to benefit infected fetus and are also used to treat the newborn after birth.

Keywords: Congenital toxoplasmosis, transmission, immune response, diagnosis, treatment.

Introduction

Toxoplasma gondii is a protozoan parasite distributed globally, causes toxoplasmosis, which is prevalent in animals (including man), birds, and soil (CDC, 2013). *Toxoplasma gondii* showed an opportunistic behavior where risk disease consequences were expected if affected a fetus or an immunosuppressed person (Peyron *et al*, 2019). But, most immunocompetent population infection pass unnoticed or with minor non-specific symptoms (as flu or a common cold) or lymph nodes affection (Saadatnia and Golkar, 2012). Serologically, *T. gondii* infection was discovered among expecting mothers worldwide with prevalence ranged from 14 to 77% (Montoya and Liesenfeld, 2004). Therefore, most countries health care programs monitored both the mother and her fetus must have an early diagnosis (Avelino *et al*, 2014). Human *T gondii* infection may be acquired: 1- ingestion of undercooked or contaminated meat containing cysts or raw vegetables (Rifaat and Morsy, 1966); 2- ingestion of oocysts dropped in cat feces on hands, food, soil, or water contaminated (Rifaat *et al,* 1976); 3- Organ transplantation (Barsoum, 2004) or even blood transfusion or needle-stick injury (Abdel-Motagaly *et al,* 2017); 4- transplacental transmission; and 5- accidental inoculation of tachyzoites (Abdel Salam *et al,* 1990). Thus, the route of human infection was either orally or congenitally (McAuley, 2014). *Toxoplasma* life cycle occurs in two hosts*:* felines as the definitive host, where the sexual reproduction took place while other mammals including man and birds serve as intermediate hosts where parasite's asexual reproduction takes place (Xiao and Yolken, 2015). Congenital toxoplasmosis was mostly transmitted from active infected mother via placenta to her fetus,

and rare in chronic mothers acquired long before gestation (El Deeb *et al*, 2012). In Egypt, serologic screening of women before or during pregnancy was done on request or for researches (Abbas *et al*, 2020). Eida *et al.* (2009) in Ismailia detected congenital infection in 14/85 fetuses by mouse inoculation, & PCR target P30 gene positive was 17 ones. They added that congenitally (16) infected newborn were asymptomatic. Tammam *et al.* (2013) in Qena reported high seroprevalence of *T. gondii* among women with first trimester abortion. They added that pregnant ones living in rural area were at a high risk for infection. Saleh *et al*. (2014) in Alexandria found *T. gondii* antibodies in 22.2% pregnant women and 20% non ones. Abdel Gawad *et al.* (2017) in Beni-Sueif by ELISA reported antibodies in 20% of 300 multiparous pregnant women. Among asymptomatic pregnancy, El-Shqanqery *et al*, (2017) in Menoufia reported 30.16% *T. gondii* seroprevalence. Azab *et al*. (2012) in Cairo among blood donors found seropositivity of 67.4% and El-Geddawi *et al*. (2016) in Alexandria reported 65.3% seropositivity with 10% with confirmed parasitemia. Besides, Saleh *et al.* (2016) on military hospital-based study declared that toxoplasmosis was occupational, nosocomial or hospital acquired infectious disease. Non-human infection, Rifaat *et al.* (1969) in Giza detected antibodies in chicken and pigeons. Rifaat *et al.* (1978) in Lower Egypt reported *Toxoplasma* antibodies in the slaughtered animals. Al-Kappany *et al*. (2010) reported >95% seroprevalence in the stray cats. Morsy *et al.* (1987) in Norte Sinai by ELISA reported *Toxoplasma* antibodies in commensal rodents. Haridy *et al.* (2010) in Greater Cairo detected anti-*T. gondii* anti bodies in working donkeys and their milk. Abdel-Hafeez *et al*. (2015) in Minia Governorate reported 50.9% seropositive in different animals processed meat. Khattab *et al.* (2022) in north western Egypt by ELISA reported 38.92% among 500-ruminants; these were camels (64.5%), sheep (43.75%), goats (27.23%), and cattle (13.46%).

Vertical transmission of tachyzoites caused subclinical or clinical lesions in developing fetuses; affecting eye or CNS and resulting sometimes in the intrauterine fetal death (Dubey, 2010). The mother mostly was infected through ingestion of food or beverages containing *Toxoplasma* tissue cysts (enclosing bradyzoites) found in improperly cooked meat or as sporulated oocysts (Robert-Gangneux and Darde, 2012) due to contamination of uncooked vegetables, fruits or water with cat feces (Djurković-Djaković *et al,* 2019). In some rare cases, she might acquire infection by transfusion of blood from an infected donor (Sarkari *et al,* 2014). During parasitemic phase, tachyzoites penetrate the intervillous space of placenta. After crossing it and escaping the trophoblastic layer (fetal epithelium), which was the 1st line of defense, it traverses mesenchymal tissues that surround fetal blood vessels (2nd defense line) before penetrating vessels (Remington *et al,* 2006).

Toxoplasma gondii tachyzoites not destroyed by mesenchymal phagocytic cells can multiply within these cells, releaseing new extracellular parasites to infect other cells, finally infecting endothelial cells lining fetal vessels embedded in the villous chorion, the chorionic plate or the umbilical cord and gaining access to the fetal circulation (Robert-Gangneux *et al,* 2011).

Transplacental transmission: Several factors can affect transplacental transmission and determine the possibility of development of congenital toxoplasmosis infection.

Gestational age: Fetal infection rate and the resulting congenital and neonatal infection severity can be correlated to the gestational stage; at late pregnancy, the risk of fetal infection is increased, while a more serious affection of the fetus can occur in the first trimester (Villard *et al,* 2016). During the first trimester of pregnancy, the intervillous space of placenta is not patent due to trophoblastic blockage of the spiral arteries, thus, less likely for *T. gondii* to get transmitted to the fetus. Actually, only after the 12th week of pregnancy does the maternal blood

supply become continuous and diffuse across the entire placenta (Jauniaux *et al,* 2003). Accordingly, when the mother gets infected during the third trimester of pregnancy, congenital toxoplasmosis occurrence is substantially more common (Rabilloud *et al,* 2010). But, the highest risk of severe fetal affection (lower incidence) was when the mother acquired infection early in pregnancy (Koga and Mor, 2010). Thus, the transmission rates of congenital toxoplasmosis varied noticeably according to the gestational trimester if the mother got infected; the first trimester (below 6%), the second trimester (22-40%) and the third one (58-72%). In the final weeks of pregnancy and just before birth, the transmission rate was at its highest levels (Montoya and Remington, 2008).

Toxoplasma gondii genotypes: Three known genotypes were recognized among human congenital infection (Kieffer *et al,* 2011). Genotype II is predominant in European and North American countries, other two genotypes, I & III are predominant in South America and Africa (Peyron *et al,* 2016), if this predominance was due to differences in genotypic distribution globally or due to an actual difference in congenital transmission capacity. However, rare cases of congenital transmission in chronically infected mothers can be explained by reinfection with another strain carrying a different genotype, for which there was no cross-immunity, during gestation (Elbez-Rubinstein *et al,* 2009). So far, no strong evidence of a link between *T. gondii* genotypes and congenital infection has been found.

Maternal load: Congenital toxoplasmosis occurs most commonly during the parasitemia phase of an acute infection or in a course of a reactivated infection with immunosuppressive patients such as immuno-deficiency virus (HIV), but rare in chronic infections as circulating tachyzoites were difficult to be recognized (Lago *et al,* 2007).

Maternal immunity: This immunity might function as hindrance to infection transmission and disease development in fetus and/or newborn, when maternal IgG antibodies travel via placenta, they diminished parasitemia in placenta and developing fetuses (Redline, 2006).

Maternal co-infection: Women who have acquired HIV infection are at risk of reactivating the dormant *T. gondii* infection and transferring the parasite to the fetuses, however, unexpectedly, this appears to be uncommon (Montoya and Remington, 2008).

Fetal/neonatal capacity of developing immune response: Development of innate and/or specific immune response(s) has a critical role in preventing or limiting the realization of a fetal/neonatal *Toxoplasma* infection. Actually, early in life, immunological responses show limited efficacy due to the relative immaturity of the immune system (PrabhuDas *et al,* 2011). The earlier newborn cases of congenital toxoplasmosis showed a limited *Toxoplasma*-specific immune response (McLeod *et al,* 1990), but others showed that the neonates, and young children (Ciardelli *et al,* 2008), and the acquired specific T-helper type 1 (Th1) responses evolving as the infected adults (Chapey *et al,* 2010).

Fetal sex: It seems there is no link between the gender of the fetus and congenital infection development (Freeman *et al,* 2005).

Clinical presentations: Congenital toxoplasmosis is an acute infection and in 85-90% of cases were asymptomatic at birth if the mother got infected during the 3rd trimester of pregnancy (Remington *et al,* 2006). Late transmission limits the period for parasite replication in fetuses/neonates, resulting in less clinically detectable damage. Clinical signs can arise days, weeks or even months after delivery. Congenital toxoplasmosis in acute infections in pregnant women causes serious health problems to fetus, including mental retardation, seizures, blindness, and death. Manifestations of congenital toxoplasmosis may not become apparent until the second or third decade of life therefore; serologic diagnosis must be confirmed at a reference laboratory before treatment with toxic drugs must be in mind (Jones *et al,* 2001).

Also, infection caused brain calcifications and hydrocephalus, frequently seen in-utero by ultrasound echography and in psychomotor impairment (Melamed *et al,* 2010).

In untreated cases, death occurred only days after birth (Remington *et al,* 2006). Abortion and stillbirth rates, though possible, appear to be uncommon in such congenital parasitic infections; however, this was not determined. Asymptomatic congenital toxoplasmosis appeared at birth can cause severe delayed forms of chorioretinitis decades later (Wallon *et al,* 2004). Lesions discovery by screening using fetal ultrasound can signal poor prognosis that can consequently lead to pregnancy termination. Encountering serious newborn forms with severe cerebral damage was rare (Berrébi *et al,* 2007). Treatment of children with neurological signs (hydrocephalus, convulsions, aberrant muscle tone) as soon as possible were significantly improved the prognosis and led to nearly normal outcomes (McLeod *et al,* 2006).

Diagnosis: Congenital toxoplasmosis is usually asymptomatic or showed nonspecific symptoms, thus laboratory serological tests, PCR and biological tests or animal inoculation were essential to detect infection (Pleyer *et al,* 2019). Late clinical squeals always appeared even years later that was why negative laboratory results didn't exclude congenital infection (Bobić *et al,* 2019). Serological screening like ELISA can test a large number of samples, while low-cost tests as IHAT limited scale screening (Villard *et al,* 2016). Further confirmation was obtained by dye test, IFAT, immunoblotting, IgG-avidity, PCR, animal inoculation with fluids as cerebrospinal fluid (Maldonado *et al,* 2017).

Diagnosis in pregnant women: Prenatal screening programs were established in countries with high levels of toxoplasmosis infection as France in 1978 (Cornu *et al,* 2009). Different countries like Austria and Slovenia find applying prenatal screening cost-effective (Binquet *et al,* 2019). Finding acute infections as soon as possible allowed the early treatment of infected mothers to prevent fetal transmission or limit consequences and fetal deaths (Wallon *et al,* 2013). Basic screening included immunological of pregnant women sera and monitoring fetal ultrasonography in case of suspicious results, amniocentesis is resorted to, while in negative results, follow-up continues (Hampton, 2015).

However, most countries worldwide perform screening for toxoplasmosis in expecting mothers if indicated. This can be of particular importance in mothers practicing high-risk activities like breading cats or preferring rare cooking (Ratha, 2020). Infection usually passed unnoticed, any clinical signs or symptoms of maternal infection as cervical lymphadenopathy necessitate investigation history of old infection in immunosuppressed females, for reactivation (Montoya and Liesenfeld, 2004). Any suspicious fetal ultrasound, calls for investigation (Moncada and Montoya, 2012). But, Elbez-Rubinstein *et al.* (2009) reported that mothers with old infections transmitted toxoplasmosis if they were re-exposed to more virulent strains.

The first step was to determine the mother's infection status; whether she was *Toxoplasma* naïve, with latent infection (long before gestation) or with a current acute infection (started during or 3 months before pregnancy). Fetal infection risk peaks in mothers in the acute phase or immunosuppressed ones with latent infection. In such cases, investigations must be done to determine the mother's immune status, infection time and anti-*Toxoplasma* drug received. These factors altered the subsequent results of laboratory tests (Pomares and Montoya, 2016), and directed to plan to save time for early treatment to avoid transmission (Olariu *et al,* 2011).

Serology is the standard for *Toxoplasma* screening pregnant women sera, mainly to detect IgG & IgM antibodies. The IgM antibodies required a week to appear with level peak in 1-3 months and then decreased gradually to the negligible or normal level. This occurred by the 10^{th} month post-infection, although in 9%- 27% of infected individuals IgM persisted for 2 or more years (Gras *et*

al, 2004). IgG was detected 2 weeks post-infection, to reach a maximum level after 3 months and decreased by the 6th month post-infection (Ratha, 2020). But, the presence of latent cysts in muscles, brain and eyes maintain a lifelong detectable level of IgG denoting previous exposure and immunity, while IgM detection usually raises suspicions of acute infections. IgA peaks a bit later than IgM and remained for 3 - 4 months (Kalem *et al,* 2022). Broadly, if IgG and IgM were undetectable, the mother is considered uninfected. If IgG was detectable but not IgM, latent infection was suspected. If IgG and IgM markers were detectable, a current infection was possible. Care was needed while analyzing the results of various tests as false results was common (Hampton, 2015). For instance, sometimes IgM might be undetectable in acute infections, a French report documented this rare form of atypical seroconversion (0.58% among infected mothers), with possible grave fetal consequences due to delayed treatment (Fricker-Hidalgo *et al,* 2013). However, others reported that 60% of IgM was not related to acute infections; identifying 20% as non-specific false-positive results and 40% as chronic infections (Liesenfeld *et al,* 2001b; Dhakal *et al,* 2015). So, at least after 2-3 weeks, a second confirmatory serological testing was required to detect seroconversion to IgG or IgA appearance (Gutierrez *et al,* 1997). More specific confirmatory tests was used, like a dye test or immunoblotting (Lesle *et al,* 2011). Praharaj *et al.* (2001) in India reported bad obstetric outcome (patients with history of repeated abortions, still births and giving birth to babies with congenital abnormalities) was one of the commonest presentations of *Toxoplasma* infection during pregnancy. Nogareda *et al.* (2014) in France reported that repeated monthly testing continues during pregnancy in high-risk was a must. Paquet and Yudin (2013) in Canada reported that rising IgG titer after 2 weeks, four folds higher than that of initial results diagnosed acute infection.

Sabin Feldman dye test: It was considered the reference and gold standard serological test for diagnosis (Sabin and Feldman, 1948) and was previously used in Egypt (Rifaat *et al,* 1965: Wishahy *et al*, 1972). Although the Sabin-Feldman dye test the gold standard to detect human toxoplasmosis, yet is done only in reference laboratories due to using live *T. gondii* virulent strain (Dunay *et al,* 2018). Laboratory diagnostic tests were established, including the commonly used serological assays such as direct or modified agglutination test (DAT/MAT), indirect hemagglutination test (IHA), enzyme-linked immunosorbent assays (ELISA), indirect immunofluorescent test (IFAT), immunochromatographic tests (ICT), latex agglutination test (LAT), and western blot (Ybañez *et al,* 2020).

IgG avidity test: Suggestive maternal serology mandates evaluating the possibility of fetal or neonatal infection, so as to start treatment as soon as possible (Saso *et al,* 2020). The first risk evaluation step would be further serological tests that can point to maternal infection timing. IgG avidity testing can be applied to help time maternal infection and assess trans-placental transmission risk (Candolfi *et al,* 2007). It was found that IgG antibodies mature over time; binding *Toxoplasma* antigen with higher avidity after 4-5 months of infection (Liesenfeld *et al,* 2001a), and persist for years in blood. Thus, high avidity can point out old infection (4-5 months prior or more). This can be of a great exclusive value of acute infection and fetal transmission in the first trimester or early second trimester, even in women with prolonged IgM response after primary infection, but a high avidity in 3rd trimester must be indecisive and might arouse unnecessary concerns and investigations. In contrast, low avidity results in the 1st trimester need follow-up, if a marked increase occurs, this requires performing an amniocentesis, but if it remains low and stable, low risk is expected and possible old infection was the cause. Low avidity in third trimester was an alarming of infection (Teimouri *et al,* 2020).

Fetal ultrasonography: Unfortunately, fetal

ultrasound might be the first thing to point out toxoplasmosis in absence of obligatory screening programs. Suspicion was suspected by severely fetal development (Hohlfeld *et al,* 1991), severe fetal growth restriction, increased placental thickness, unexplained increase in amniotic fluid, fetal anomalies like calcifications, ascites or hydrocephalus (Esteves *et al,* 2022). Although not for early exclusion, fetal ultrasound can detect clear fetal abnormalities late in infection; preferably used as a monitoring tool for fetal development in suspicious or diagnosed acute maternal infections (Malinger *et al,* 2011. Detected abnormalities can involve the CNS, liver, spleen or kidney. Findings like hydrocephalus, ventriculomegaly and intracerebral calcifications or ascites was seen (Hampton 2015). Worsening lesions can lead to a decision of an earlier delivery and a neonatologist follow-up is required (Ratha, 2020).

Amniocentesis & PCR: To confirm or exclude fetal infection, PCR, done on sampled amniotic fluid to diagnose intrauterine infection and considered the gold-standard (de Oliveira Azevedo *et al,* 2016). Timing of performing such a test affects the accuracy of the results; the sample might not contain the parasite, even with the presence of actual infection, except after the 18^{th} week of gestation due to fetal incapability to excrete it yet (Serranti *et al,* 2011). Besides, before that, there was a greater risk of inducing preterm labor by procedure (Kalem *et al,* 2022). Also, during 3^{rd} trimester, amniocentesis is considered a high-risk practice and negative results were not exclusive (Sterkers *et al,* 2012) as a month at least must have passed after suspected maternal infection for the parasite to reach the amniotic fluid, in addition to the dilution of amniotic fluid in the 3^{rd} trimester (Thalib *et al,* 2005). Besides, if the expecting mother received pyrimethamine-sulphonamides combinations before doing the test, it can yield negative results (Rabilloud *et al,* 2010). This is particularly common due to empirical treatment without performing amniocentesis; in situations like the lack of facilities, parents' refusal or fear of preterm labor (Wallon *et al,* 2010).

Quantitative PCR on amniotic fluid is only used as a research tool till now. A study confirmed that the earlier the infection time (< 20^{th} week of pregnancy) and the higher the parasitic load (≥100/mL), the more severe congenital infection symptoms were (Romand *et al,* 2004). Also, amniotic fluid can be used in some reference laboratories for direct detection and definite diagnosis and isolation by culture, staining and microscopic detection (Shehu *et al,* 2019).

Neonatal diagnosis: If a maternal serology or fetal ultrasound showed any abnormality, prompt neonatal investigations must be done after delivery to confirm or exclude the congenital toxoplasmosis (Pomares and Montoya, 2016), as after the age of one, there was a possibility that positive results reflected a postnatal infection (Pleyer *et al,* 2019).

Screening at delivery: At birth, screening for *Toxoplasma* in placenta or cord blood serum can be beneficial (Fricker-Hidalgo *et al,* 2007). Placental studies using PCR (Robert-Gangneux *et al,* 2010) or by mice sub-inoculation (of current limited use) show a quite high specificity (>92%) rather than sensitivity (Robert-Gangneux *et al,* 2011). However, positive placental PCR might be the result of primary placental infection without any transmission to the fetus (Villard *et al,* 2016). PCR on cord blood was no longer preferred practice (specificity up to 100%) due to its quite low sensitivity (Sterkers *et al,* 2012).

Clinical and radiological assessments: On primary examination of infected babies 85% may appear quite normal; however intracranial calcifications, hydrocephalus and chorioretinitis represented the classic triad for congenital infection suspicion, without pathognomonic presentation. Urgent detailed ophthalmological, neurological and hearing assessments were required and can be considered diagnostic if no other etiology was observed clinically. Neuroimaging (cranial ultrasound and magnetic resonance imaging (MRI)) can also reveal microcephaly, corti-

cal atrophy, microphthalmia and assess the aqueduct state and hydrocephalus risk. Also, ocular lesions might be the only sign of congenital toxoplasmosis and examination must be repeated even in adulthood, for the risk of delayed eye lesions (Saso *et al,* 2020).

Serological assessment: Even if amniocentesis PCR proved positive, a neonatal serological study is crucial to exclude false-positive PCR results (Moncada and Montoya, 2012). Serum samples from maternal and newborn origin should be compared for IgM, IgA and IgG anti-*Toxoplasma* antibodies (Murat *et al,* 2013). Diagnosis must is a if the maternal level was four times or more in infant's serum (Khan and Khan, 2018).

IgG antibodies transfer passively from the mother during gestation (Teimouri *et al,* 2020). Their level in newborn serum was the gold standard for congenital toxoplasmosis diagnosis. If they were of maternal origin, they should decrease gradually throughout the first 6 months and disappeared before first year of age (Remington *et al,* 2010). However, their persistence beyond one year was diagnostic (Shehu *et al,* 2019).

As for IgM and IgA detection, caution with results interpretation is needed. There was a risk of maternal antibodies contamination for the first 5 days (IgM) and the first ten days (IgA) of life. Thus serum sampling must be done after ten days from birth to distinguish neonatal from maternal antibodies (Magi and Migliorini, 2011). Also, it must be done 2 weeks after the last blood transfusion to avoid false-positive results (Maldonado *et al,* 2017). Combining results of the IgM and IgA, in comparison with IgG, was preferred due to increasing sensitivity than each test done alone (Montoya, 2002). However, up to 50% of infants have no detectable IgM and IgA in the first 30 days of life due to delayed seropositivity especially if the maternal infection occurred late in the gestation (PHWHP, 2018) or due to disappearance of antibody response with long time interval in early fetal infection (Gilbert *et al,* 2007). Moreover, any treatment during gestation or early after birth may arrest the serological response and results in false-negative results. Thus, re-assessment after treatment cessation is needed (Peyron *et al,* 2019). So, repeated assessments at first and second months, then every two months is a necessary follow-up. Immunoglobulin E (IgE) use appears defective compared to higher diagnostic value of combined IgM and IgA (Pomares and Montoya, 2016).

Western blotting: Shortly after birth, reference laboratories can resort to western blotting of IgG, IgM and IgA in maternal and neonatal sera (Machado *et al,* 2010). Western blotting increased the sensitivity of the serological assessments (Murat *et al,* 2013) up to 95.8% compared to western blotting or serology alone (L'Ollivier *et al,* 2012). It showed the ability to establish congenital infection diagnosis 3 months earlier than serology alone (di Carlo *et al,* 2011). Band patterns comparison revealed neonatal endogenous antibodies, not detectable in the mother's serum (Pomares and Montoya, 2016). Also, increased intensity of certain bands in the infant's serum compared to that of his mother can point to the diagnosis. Comparing IgM patterns was used to exclude maternal contamination of cord blood during labor (Villard *et al,* 2016).

Lumbar puncture: PCR can be done on neonatal CSF obtained by lumbar puncture added to peripheral blood and urine (Olariu *et al,* 2014). CSF assessment for protein, glucose and cell count can point out increased protein content and pleocytosis in infected babies (Saso *et al,* 2020).

Thus, a neonatal infection can be confirmed by positive IgM and IgA ten days after birth, positive animal inoculation from amniotic fluid or cord blood, and detection of anti-*Toxoplasma* IgG after a year of age or positive PCR results confirmed by serological findings association (Bobić *et al,* 2019). Besides, studies revealed the potential usefulness of assessing IgG orally and interferon-gamma released from T cells stimulated by *T. gondii* (Pomares and Montoya, 2016;

Villard *et al,* 2016).

Treatment: To lower the risk of congenital toxoplasmosis, symptomatic and asymptomatic expected mothers diagnosed with an active *T. gondii* infection must receive anti-mic-robial therapy directed against *T. gondii* (Esteves *et al,* 2022).

Spiramycin, a macrolide antibiotic, is considered a maternal therapy with potential fetal prophylaxis abilities. Although it is a parasitostatic treatment that cannot cross the placental or enter the brain tissues, it was continuously used during acute maternal infections, especially with negative amniocentesis results, as it accumulates in placental tissues, thus hindering the transmission from the infected placenta to the fetus. Besides, pyrimethamine-sulphadiazine combination, as a parasiticidal treatment, can cross the placenta and infiltrate the brain tissues; hence, it is used to treat proven fatal infections. Treatment can extend from 12 to 24 months. Nevertheless, in Germany, some centers individualize the regimen according to the severity of infection to be 3, 6 or 12 months (Maldonado *et al,* 2017).

The use of pyrimethamine and sulphadiazine combination is considered the gold-standard treatment; pyrimethamine (phenylpyrimedine) a repositioned antimalarial drug and sulphadiazine (a sulphonamide). It was proved that combining the two drugs has a synergistic effect (multiplies their individual potencies eight times). This combination usually gave the potential to resolve signs of active infection in a few weeks (Serranti *et al,* 2011). In neonates, treatments showed >72% improvement of the severe neurological symptoms while protecting cognitive and hearing functions (McLeod *et al,* 2006).

Although performing amniocentesis is critical in planning treatment, treatment can be initiated even before performing the test as the highest potency in preventing or reducing neurological damage in the fetus was expected if drugs are administered in the 3 week-gap following maternal seroconversion (Esteves *et al*, 2022). Mothers suspected to have an acute infection are treated with spiramycin in the first trimester, spiramycin or pyrimethamine combination with sulphonamides (sulphadiazine or sulphadoxine) in the second trimester or just pyrimethamine-sulphonamide treatment in the 3rd trimester (Serranti *et al,* 2011). The positive amniocentesis results necessitate shifting to pyrimethamine sulphonamide combination, but with a negative test result, spiramycin therapy is maintained until delivery to protect against placental transmission. Azithromycin was a possible substitute for sulphonamides in case of intolerance. Furthermore, monthly ultrasound or brain MRI is needed for fetal follow-up (Peyron *et al,* 2019). Also, on using pyrimethamine, it was usually supplemented with leucovorin (folinic acid, and not folic acid), to guard against the effects of dihydrofolate reductase enzyme inhibition; resulting in lower folic acid levels and bone marrow depression (Derouin *et al,* 1992). This explained why the pyrimethamine-sulphadiazine regimen is preferably used in the third trimester to avoid any teratogenic effect in earlier gestational stages. In case of developing maternal neutropenia, treatment is ceased for a short time, while maintaining leucovorin therapy, until normal neutrophils level was restored, then the therapy was resumed (Peyron *et al,* 2019). Mothers were usually advised to consume more fluids with sulphonamides treatment, and also, alkalization of urine is necessary (Leekha *et al,* 2011). In Denmark, only 14% suffered from pyrimethamine and sulfadiazine side effects (Schmidt *et al,* 2006). Nevertheless, in case of old maternal infection or infection contracted three months prior to pregnancy, there is no or limited fear of fetal transmission, except if the mother gets re-infected with another *Toxoplasma* strain or is severely immunocompromised with the risk of reactivation. In both situations, to administrate anti-*Toxoplasma* therapies were indicated (Maldonado *et al,* 2017).

Gratefully, after managing acute infections, treated infants can lead a normal life

but care during pregnancy or after ocular trauma is required to monitor against activation of chorioretinitis as these drugs destroy active stages (tachyzoites) but without effect on (bradyzoites) in the brain cysts or chronic eye lesions (Garweg *et al,* 2005). Clinical, ophthalmological and serological assessments should be carried on regularly in the first three years of life and yearly till the age of ten; some advocate for life (Peyron *et al,* 2011; Serranti *et al,* 2011). Some countries allow pregnancy termination in an ultrasound-proved severe fetal state of deterioration or anomalies like hydrocephalus. Inducing early labor or even cesarean section proved non-significant in decreasing the risk of infection transmission (Dhombres *et al,* 2017).

As to toxoplasmosis sero-negative pregnant mothers, Maldonado *et al.* (2017) in the United States reported that if an infected mother showed negative serological results, especially in the third trimester, treatment was not an easy option and required parental approval Dunay *et al.* (2018) in Germany reported that treating asymptomatic newborns prevented ocular toxoplasmosis. But, Peyron *et al.* (2019) in France reported that 79% of negative sero-neonates with fear of treatment the mothers might hide serological changes proving infection, thus repeated serological follow-up was a must at shorter intervals with 3rd trimester infections.

Other drugs: Clindamycin®, Cotrimoxazole®, Dapsone®, Atovaquone® and Clarithromycin® were used as alternative treatment for congenital toxoplasmosis (Zhang *et al,* 2018), with cotrimoxazole cured eye lesions in infants (Márquez-Contreras, 2018).

Azithromycin and combined spiramycin and cotrimoxazole decreased vertical transmission risk to fetus, especially cotrimoxazole (Valentini *et al,* 2009). But, sulfonamide displaced bilirubin from its albumin-binding sites in plasma led to an elevation of plasma bilirubin that crossed blood-brain barrier, reaches central neurons to cause kernicterus (Thyagarajan and Deshpande, 2014).

Atovaquone is an antimalarial safe and effective against tachyzoites and bradyzoites decreased vertical toxoplasmosis transmission (Oz, 2014). It is a well-tolerated drug as an effective alternative for toxoplasmosis patients who didn't tolerate standard therapies (Kovacs, 1992). The nontoxic diclazuril *in-vivo* was superior to atovaquone in controlling symptoms (Oz and Tobin, 2014).

Nevertheless, the TOURCH fevers must be considered in the congenital toxoplasmosis differential diagnosis (Morsy *et al,* 2022)

Conclusion

Toxoplasmosis is one of the commonest parasites worldwide exhibited latency abilities, flaring up risks with immune suppression and hazards of neurological and multisystemic affection on congenital transmission. Congenital toxoplasmosis can be treated and prevented, by early diagnostic test(s).

But, one may ask: 1-Does parasitic genotypic variation explain the variability seen across the globe in disease prevalence and severity? 2- Are there better treatment options available, to prevention of transmission from an infected pregnant woman to her fetus and to treat congenitally infected children, especially newer drugs that showed activity against related parasites?

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