ROMANIAN SOCIETY OF PREVENTIVE MEDICINE

Ro J Prev Med. 2023, sept; 2 (3): 12–21

TOXOPLASMOSIS AND PREGNANCY: CURRENT APPROACHES FOR FAVOURABLE FETAL OUTCOME

Cristiana-Elena Durdu[1], Roxana-Elena Bohîlțea[1,2]

[1]Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
[2]Department of Obstetrics and Gynecology,''Carol Davila'' University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Toxoplasma gondii is one of the most widespread parasites worldwide. Although it causes asymptomatic infections in most cases, it can lead to severe disease in immunocompromised individuals. When acquired during pregnancy, it can negatively impact fetal development, resulting in unfavorable outcomes in neonates. The epidemiology of this parasite varies from country to country, leading to a lack of international consensus on screening, diagnosis, and management of congenital toxoplasmosis. This article aims to review aspects related to the modes of transmission, screening, fetal prognosis, management, and prevention of this infection to increase the chances of a favorable fetal outcome.

Keywords: *congenital toxoplasmosis, prenatal screening, Toxoplasma gondii*

Introduction

Being one of the most successful infectious agents, Toxoplasma gondii is a protozoan parasite that infests most warm-blooded organisms, including humans (1). Chronic toxoplasmosis is present in about 30% of the world population (2). For the majority of patients, there are no manifestations of the disease. However, for immunocompromised patients and babies, the condition can have disastrous consequences (3). Some of the effects of pregnancy-acquired toxoplasmosis are represented by postnatal disabilities and fetal demise (1). In over 80% of cases, the disease causes no symptoms. However, when manifestations of the disease appear, they are uncharacteristic and non-severe and include an episode of elevated body temperature during 2-3 days, shivers, perspiration, cephalalgia, hepatosplenomegaly, muscle pain, pharyngitis, and a disseminate nonpruritic maculopapular skin eruption. The most frequent manifestation of the disease is represented by lymphadenopathy, which is present in 7% of pregnant women with acute toxoplasmosis. Although extensive lymphadenopathy occurs in a small number of cases, it usually lasts a few weeks, appears in the cervical region symmetrically, is unpainful and nonfluctuant, and the adenopathy size is under 3 cm. Another complication of the disease, which can lead to blindness or visual impairment, is represented by chorioretinitis (4). Congenital toxoplasmosis can have severe consequences for the fetus. However, there are countries where toxoplasma screening is not recommended, even though screening and diagnosis techniques are available. Consequently, Toxoplasma infection in pregnancy is often neglected, and specific recommendations for patients at risk are not made, even though the implications of vertical transmission are of great importance (5).

Transmission Modalities

Toxoplasma gondii has a sophisticated reproductive cycle and has a definitive host represented by felines and an intermediate host. In definitive hosts, T. gondii expresses a sexual cycle,

and in intermediate hosts, it undergoes an asexual process (6). In intermediate hosts, the active form of Toxoplasma gondii, represented by tachyzoites, can transform into a dormant state represented by bradyzoites, usually located in organs like the brain and eyes. Consequently, this inactive form of Toxoplasma gondii is challenging to eliminate by the immune system or drugs that cannot pass the blood-brain barrier or the multiple layers of the ocular globe (7–10). Ingestion of the bradyzoites by the definitive hosts is followed by several cycles of asexual reproduction and, finally, by sexual reproduction, which leads to the formation of unsporulated oocysts. Next, unsporulated oocysts are eliminated through feces and become infectious, which can contaminate the soil, fruits, vegetables, and water and can be ingested by intermediate hosts such as pigs, cows, and sheep (11,12). The transmission modalities of Toxoplasma gondii to pregnant women described in the literature are represented by ingesting contaminated fruits, vegetables, water, seafood, unpasteurized milk, and undercooked meat (10,13–16).

During pregnancy, Toxoplasma gondii can be transmitted to the fetus if the mother has an acute infection with the passage of the parasite through the placenta. Studies showed that transmission probability varies with gestational age: 56% at 30, 23% at 18, and 2.2% at six weeks of gestation (17). The transplacental mean transmission rate of maternal primary infection is 40% (18). Another possible scenario is represented by maternal reinfection with a different strain. However, this probability is very low since only several cases are described in the literature (19,20). In immunocompromised patients, such as HIV-infected individuals, there is a possibility of reactivation of an old maternal infection, although studies have demonstrated that this possibility is negligible or absent (21,22). Concerning the vertical transmission of an infection acquired before pregnancy, the probability is very low, as only a small number of cases of transmission of an infection developed one or two months preconceptional have been described (23). In Europe and the USA, the incidence of fetal infection with Toxoplasma gondii varies from 1 to 10 cases per 10,000 live births (24).

Effects on the Fetus

Congenital toxoplasmosis has a wide range of manifestations, the severity depending on the moment of acquisition of the infection. In the first trimester, it can lead to miscarriage, mental disability, hydrocephaly, or ocular lesions. In contrast, congenital toxoplasmosis is associated with a less severe outcome in the second and third trimesters, as the infection is often subclinical (12,25,26). Reducing severity during advancing gestational age may be attributed to the maturation of the fetal immune system (26). It is estimated that 90% of cases of congenital toxoplasmosis in France are asymptomatic. Two-thirds of the remaining cases present with moderate disease (peripheral chorioretinitis, brain calcifications), and one-third present with severe disease (generalized disease, severe ocular lesions, hydrocephalus) (27). Other disease manifestations can include ophthalmic calcifications, thrombocytepenia, hepatomegaly, encephalomyelitis, central nervous system necrosis and calcification, low birth weight, jaundice, and meningoencephalitis (28).

Fetal impairment can be evaluated with ultrasound. There are some characteristic ultrasound signs that can be identified, such as intracranial calcification, advancing ventricular dilatation, and periventricular abscesses. Additionally, there are some less frequent ultrasound signs, such as shortened corpus callosum, periventricular echogenicity, cortical gyration lesions, lenticulostriate vessel vasculitis, cerebellar impairments, and subependymal modifications (cysts, echogenicities) that can be observed (29). Intracranial ultrasound aspects can be isolated, or they can be associated with other intracranial factors or with extracranial elements such as being small for gestational age, hepatomegaly, ascites, hyperechogenic bowel, splenomegaly, and placentomegaly (29). Since

ultrasound anomalies can appear after an interval of a few months following maternal infection, there is a strong need for serial ultrasound evaluations. This tool is essential not only for predicting the fetal outcome but also for visualizing ultrasound signs associated with toxoplasmosis, which can raise awareness and indicate toxoplasmosis testing in countries where screening is not recommended (29).

Concerning the prognosis of these children, it is usually good, with no significant differences in development at 3-4 years compared to the general population (30). Isolated intracranial calcifications are not associated with mental disability. However, they are incriminated as a risk factor for retinochoroiditis during childhood (31,32). Isolated extracranial signs are not associated with a poor outcome (29). In many cases, the classical toxoplasmosis triad of Sabin (hydrocephalus, intracranial calcification, chorioretinitis) is absent in neonates, although neural or eye lesions can develop later in life when the disease remains undiagnosed and untreated (33).

Screening Methods and Diagnostic Approach

In some parts of the world, such as the UK, USA, Canada, and some parts of Europe, Toxoplasma gondii screening is not recommended due to the low incidence of the disease and the high screening costs (34–36). On the other hand, there are some European countries where Toxoplasma screening is included in prenatal routine tests and is recommended monthly, once every two or three months (4,37). Due to more virulent strains and population risk factors in South America, Brazil is also encouraged by the authorities to include Toxoplasma screening of pregnant women in medical practice (38).

Screening for toxoplasmosis in pregnancy is based on serological testing since the infection is asymptomatic in the majority of cases (25). The methods frequently used involve measuring IgG and IgM antibodies. IgM titers rise after 1 week of acquiring the infection and can remain at high levels for months and even years after the infection. Consequently, IgM titers cannot be used to diagnose a recent infection (1). IgG titers reach a maximum level 6 to 8 weeks after infection, and antibody levels decrease over the next two years but remain positive (39). The presence of IgG antibodies indicates that an infection has occurred, but this test does not provide any information about the moment when the mother acquired the parasite. In some clinical scenarios, additional tests might be needed, such as IgA and IgE antibodies. IgA antibodies appear faster than IgM antibodies and can last a few months. Due to the short duration of IgE antibodies, they could be more helpful in identifying a recent infection (1).

After serological testing, we can have four clinical scenarios:

- Nonreactive IgG and nonreactive IgM: The patients never had the infection. In this situation, the patient must be informed about the general prevention methods, and serological screening must be continued (12).
- Nonreactive IgG and reactive IgM: An acute infection is suggested. This situation requires the repetition of antibody testing after 2-3 weeks. The appearance of IgG antibodies confirms the diagnosis. In the persistent absence of IgG antibodies, high levels of IgM could signify a false-positive IgM result, which can occur in the context of antinuclear antibodies, rheumatoid factor, and nonspecific binding in vitro. This situation requires supplementary tests such as ELISA or Immunosorbent Agglutination Assay (ISAGA) (40).
- Reactive IgG and reactive IgM: An acute infection is suggested. This situation requires repeating antibody testing and IgG avidity testing after 2-3 weeks (25).
- Reactive IgG and nonreactive IgM: The infection occurred before pregnancy (12).

The IgG avidity test is used to differentiate between an acute or chronic infection (41). During a Toxoplasma gondii infection, the avidity of parasitic antigens to different antibodies varies. For

example, in a recent infection, the avidity is low; in an old infection, the avidity is high (25). This test has limitations since low avidity can persist for several months after the infection. Consequently, while a high avidity result suggests an old infection, a low or intermediate avidity result cannot be used to diagnose a recent condition (25,42,43). The long persistence of low avidity after infection can have several explanations. It has been suggested that antiparasitic treatment reduces the parasitic load and postpones the increase in the avidity index (44,45). Significant inter-individual differences have been noted, and in some cases, a low avidity index could not be explained (44,45). A high avidity result rules out a recent infection with a positive predictive value of almost 100% (46–50). Depending on the laboratory, a past infection is defined as an infection older than 3, 4, or 5 months (25). On the other hand, a low avidity result cannot be used to diagnose a recent infection, with the positive predictive value varying between 61.1% to 69.9% depending on the test used (46,49–53). However, some authors suggest that a very low avidity result could strongly suggest a recent infection. For example, results lower than 15% with the Elecsys assay or lower than 17% with the Architect assay could make a reliable diagnosis for infections of less than 3 or 2 months, respectively (46,49). Repeated serology testing after 2-3 weeks following a very low avidity result is obtained is required until additional studies are ruled out in order to confirm a recent infection (25). A high avidity result in early pregnancy is indicative of an old infection. In this situation, Toxoplasma gondii screening can be discontinued if the antibody titers remain stable upon a second determination 3 weeks later. Special consideration must be given to a high avidity result at the end of the first trimester, as there can be a scarce situation of an infection acquired periconceptionally, and the result must be interpreted with caution (54,55). Avidity testing results in the second and third trimesters are more complex than in the first. A high avidity index determined four months after conception is unreliable in diagnosing a past infection. In this situation, supplementary tests are needed to confirm a recent infection (12). It has been suggested that the presence of IgA antibodies in combination with IgG and IgM antibodies is more suggestive of a recent infection than the presence of IgG and IgM antibodies in the absence of IgA antibodies.

Moreover, it was shown that the IgA titer decreases as the IgG avidity index increases (56). This category of patients could receive amniocentesis, ultrasound follow-up, or medical treatment based on individual assessment (12). In the case of an intermediate avidity index, the management becomes more difficult. When this type of result is obtained in the first trimester, it might be helpful to repeat the test using another testing method available on the market, hoping that it will yield a high avidity result. When the second determination of antibodies, conducted two to three weeks after the initial decision, shows stable titers, an intermediate avidity result is interpreted as a past infection. Otherwise, a recent infection cannot be excluded, and the management requires antiparasitic treatment and fetal testing (50,57,58). In the case of a low avidity result, especially if it is a shallow result, a recent infection cannot be excluded and requires immediate action, including medical treatment and fetal testing (46,59).

When maternal infection is confirmed, fetal testing is required and can be performed through PCR from amniotic fluid or parasite isolation from the amniotic fluid (60). Amniocentesis should not be completed before 18 weeks and within 4 weeks from the presumed Toxoplasma gondii infection. The probability of false negative results increases if amniocentesis is performed before this period due to the possibility of postponed passage of Toxoplasma gondii through the placenta (61). A positive impact from amniocentesis alone is not an indication of the termination of pregnancy (12).

Management Strategies

At the moment, the most common therapeutic regimens include spiramycin, sulfadiazine with

pyrimethamine, and sulfamethoxazole with trimethoprim. Alternative regimens include epiroprim and atovaquone (62). The French Multidisciplinary Working Group recommends two types of medical treatment protocols. Type 1 protocol includes spiramycin 1 g three times per day (12). Due to the fact that spiramycin accumulates at the placental level, it was suggested that if initiated early enough, it can reduce the chances of vertical transmission (63). On the other hand, it has no effect on established parasitosis (64). Type 2 protocol includes a combination of 50 mg of pyrimethamine once a day, 500 mg of sulfadiazine three times per day, and 25 mg of folinic acid twice per week. Alternatively, a combination of 2 capsules of Fandasir (500 mg of sulfadoxine and 25 mg of pyrimethamine) per week and 25 mg of folinic acid twice per week can be used (12).

In the first trimester, management requires spiramycin treatment as soon as possible. In the absence of amniocentesis, spiramycin must be continued until birth. Amniocentesis can be performed at 18 weeks, and a positive result requires switching to protocol 2, while a negative result requires the continuation of spiramycin In the second trimester, protocol 1 or 2 must be started immediately. After performing amniocentesis, a positive result requires protocol 2, and a negative effect requires protocol one until delivery. “In the third trimester, protocol two must be started as soon as possible and must be continued until birth in the absence of amniocentesis. If amniocentesis is performed, a negative result requires switching to spiramycin, and a positive impact implies the continuation of protocol two until delivery (12).

Prenatal monitoring must include monthly ultrasound follow-ups, with the frequency increasing to twice monthly in case of a positive result from amniocentesis. If there are challenges in interpreting ultrasound images, fetal MRI can be performed, although it is not used routinely (12). Regarding obstetrical management, termination of pregnancy might be indicated in case of severe ultrasound lesions such as hydrocephaly. Intracranial isolated lesions are not associated with a negative outcome, and they don’t represent an indication for termination of pregnancy (31). Deciding on immediate cesarean section or induction of birth is not justified since it is not proven that this management would reduce transplacental transmission of the parasite (65).

Prevention Strategies

There are several general rules that a pregnant woman can follow in order to protect herself from a Toxoplasma gondii infection. Drinking unfiltered water should be avoided as well as eating raw seafood (16). Vegetables and fruits must be washed thoroughly. Activities such as gardening, where contact with contaminated soil is possible, require responsible hand washing to avoid accidental ingestion of soil (66–68). Improperly prepared or raw meat is often a source of infection. Consequently, meat should be cooked at 66°C or higher. It has also been suggested that freezing the meat is the best way to eliminate the parasite, so the meat should be frozen at -12°C or lower for a minimum of 24 hours. Knives, cutting boards, counters, and the sink should be cleaned thoroughly after food preparation. When handling uncooked meat, pregnant women should avoid contact with mucous membranes. Pregnant individuals should avoid tasting meat while cooking (66–71). Meat from animals raised in indoor conditions has a lower chance of contamination than meat from outdoor animals (66). There is weak evidence suggesting that smoked or pickled meat might be unsafe. The risk increases in cases of specific local production methods involving the use of more than one type of meat, with insufficient drying and curing processes (66,72,73). Pregnant women who own a cat are at low risk of toxoplasmosis since cats excrete infectious oocysts only for three weeks in their life. Also, fresh feces are not contagious, although it might be a good idea to ask others to clean the litter box (66–68). For non-pregnant patients who have acquired toxoplasmosis, it is recommended to wait six months before planning a pregnancy. However, in an immunecompetent

person, the chance of vertical transmission in case of infection one to three months before pregnancy is very low (74,75).
Without optimal medical treatment, vaccines against Toxoplasma gondii represent a crucial future perspective. Several vaccine types have been studied, including DNA, inactivated, and live attenuated vaccines (76). At present, there is a single vaccine named Toxovax, which is used for breeding ewes at risk. Live attenuated vaccines represent a promising method for Toxo-plasma gondii prevention in the future (77).

Conclusion

The complex life cycle of Toxoplasma gondii makes it one of the most well-adapted pathogens for parasitic survival. Its numerous transmission methods and multiple hosts that can be infected contribute to the global spread of this pathogen. Although the infection is generally asymptomatic, it can have disabling consequences for the developing fetus. Despite significant technological progress in recent years, diagnosing the disorder during pregnancy remains challenging in certain situations, and test results are difficult to interpret. A particular problem that draws attention is the rare reactivation of latent infection or reinfection with a different strain. In the case of diagnosing an old infection (reactive IgG, non-reactive IgM), recommendations involve discontinuing screening. Therefore, these rare situations mentioned above would go unnoticed. Literature suggests that an increase in IgG antibodies with two determinations performed three weeks apart using the same technique and at the same laboratory could indicate a recent infection. Hence, our approach involves continuing screening for patients with old infections by measuring IgG antibodies. Although it is a rare condition, obstetricians should be aware of toxoplasmosis with severe complications and, therefore, instruct patients on the general protective measures to be taken. Although still preclinical, vaccines against Toxoplasma gondii represent a promising future perspective.

References

1. Liu Q, Wang ZD, Huang SY, Zhu XQ. Diagnosis of toxoplasmosis and typing of Toxoplasma gondii. Parasit Vectors. 2015 May 28;8:292. doi: 10.1186/s13071-015-0902-6.
2. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis and treatment. Expert Rev Anti Infect Ther. 2012 Jul;10(7):815-28. doi: 10.1586/eri.12.58.
3. Lima TS, Lodoen MB. Mechanisms of Human Innate Immune Evasion by *Toxoplasma gondii*. Front Cell Infect Microbiol. 2019 Apr 16;9:103. doi: 10.3389/ fcimb.2019.00103.
4. Gilbert R, Gras L; European Multicentre Study on Congenital Toxoplasmosis. Effect of timing and type of treatment on the risk of mother to child transmission of Toxoplasma gondii. BJOG. 2003 Feb;110 (2):112-20. doi: 10.1016/s1470-0328(02) 02325-x.
5. Rudin C, Hirsch HH, Spaelti R, Schaedelin S, Klimkait T. Decline of Seroprevalence and Incidence of Congenital Toxoplasmosis Despite Changing Prevention Policy-Three Decades of Cord-blood Screening in North-western Switzerland. Pediatr Infect Dis J. 2018 Nov;37(11):1087-1092. doi: 10.1097/ INF. 0000000000001978.
6. Dubey JP. History of the discovery of the life cycle of Toxoplasma gondii. Int J Parasitol. 2009 Jul 1;39(8):877-82. doi: 10.1016/j.ijpara.2009.01.005.
7. Cleary MD, Singh U, Blader IJ, Brewer JL, Boothroyd JC. Toxoplasma gondii asexual development: identification of developmentally regulated genes and distinct patterns of gene expression. Eukaryot Cell. 2002 Jun;1(3):329-40. doi: 10.1128/ EC.1.3.329-340.2002.
8. Watts E, Zhao Y, Dhara A, Eller B, Patwardhan A, Sinai AP. Novel Approaches Reveal that Toxoplasma gondii Bradyzoites within Tissue Cysts Are Dynamic and Replicating Entities In Vivo. mBio. 2015 Sep 8;6(5):e01155-15. doi: 10.1128/ mBio.01155-15.
9. Konradt C, Ueno N, Christian DA, Delong JH, Pritchard GH, Herz J, Bzik DJ, Koshy AA, McGavern DB, Lodoen MB, Hunter CA. Endothelial cells are a replicative niche for entry of Toxoplasma gondii to the central nervous system. Nat Microbiol. 2016 Feb 15;1:16001. doi: 10.1038/ nmicrobiol.2016.1.
10. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000 Nov;30(12-13):1217-58. doi: 10.1016/s0020-7519(00) 00124-7. Erratum in: Int J Parasitol 2001 Feb;31(2):217-20.
11. Zhang Y, Lai BS, Juhas M, Zhang Y. Toxoplasma gondii secretory proteins and their role in invasion and pathogenesis. Microbiol Res. 2019 Oct;227:126293. doi: 10.1016/j.micres.2019.06.003.

12. Peyron F, L'ollivier C, Mandelbrot L, Wallon M, Piarroux R, Kieffer F, Hadjadj E, Paris L, Garcia-Meric P. Maternal and Congenital Toxoplasmosis: Diagnosis and Treatment Recommendations of a French Multidisciplinary Working Group. Pathogens. 2019 Feb 18;8(1):24. doi: 10.3390/pathogens8010024.
13. Dubey JP. The history of Toxoplasma gondii—the first 100 years. J Eukaryot Microbiol. 2008 Nov-Dec;55(6):467-75. doi: 10.1111/j.1550-7408.2008.00345.x.
14. Vieira FP, Alves Mda G, Martins LM, Rangel AL, Dubey JP, Hill D, Bahia-Oliveira LM. Waterborne toxoplasmosis investigated and analysed under hydrogeological assessment: new data and perspectives for further research. Mem Inst Oswaldo Cruz. 2015 Nov;110(7):929-35. doi: 10.1590/0074-02760150262.
15. Almeria S, Dubey JP. Foodborne transmission of Toxoplasma gondii infection in the last decade. An overview. Res Vet Sci. 2021 Mar;135:371-385. doi: 10.1016/j.rvsc.2020.10.019.
16. Jones JL, Dargelas V, Roberts J, Press C, Remington JS, Montoya JG. Risk factors for Toxoplasma gondii infection in the United States. Clin Infect Dis. 2009 Sep 15;49(6):878-84. doi: 10.1086/605433.
17. Rabilloud M, Wallon M, Peyron F. In utero and at birth diagnosis of congenital toxoplasmosis: use of likelihood ratios for clinical management. Pediatr Infect Dis J. 2010 May;29(5):421-5. doi: 10.1097/ INF.0b013e3181c80493.
18. Kaye A. Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants. J Pediatr Health Care. 2011 Nov-Dec;25(6):355-64. doi: 10.1016/j.pedhc.2010.04.008.
19. Desmonts G, Couvreur J, Thulliez P. Toxoplasmose congénitale. Cinq cas de transmission à l'enfant d'une infection maternelle antérieure à la grossesse [Conge-nital toxoplasmosis. 5 cases of mother-to-child transmission of pre-pregnancy infec-tion]. Presse Med. 1990 Sep 29;19 (31):1445-9. French. PMID: 2146635.
20. Elbez-Rubinstein A, Ajzenberg D, Dardé ML, Cohen R, Dumètre A, Yera H, Gondon E, Janaud JC, Thulliez P. Congenital toxoplasmosis and reinfection during pregnancy: case report, strain characterization, experimental model of reinfection, and review. J Infect Dis. 2009 Jan 15;199(2): 280-5. doi: 10.1086/595793.
21. Dunn D, Newell ML, Gilbert R. Low risk of congenital toxoplasmosis in children born to women infected with human immunedeficiency virus. Pediatr Infect Dis J. 1997 Jan;16(1):84. doi: 10.1097/00006454-199701000-00023.
22. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. Eur J Obstet Gynecol Reprod Biol. 1996 Sep;68(1-2):93-6. doi: 10.1016/0301-2115(96)02497-9. PMID: 8886688.
23. Boumahni B, Randrianivo H, Flodrops H, Kauffmann E, Sauve F, Chauvet O, Renouil M, Fourmaintraux A. Toxoplasmose maternelle anté-conceptionnelle et choriorétinite chez des jumelles [Maternal toxoplasmosis before conception and chorioretinitis in twin sisters]. J Gynecol Obstet Biol Reprod (Paris). 2004 May;33(3):248-50. French. doi: 10.1016/ s0368-2315(04)96447-2.
24. Sato S, Nishida M, Nasu K, Narahara H, Norose K, Aosai F. Congenital toxoplasmosis from a mother with type 2 diabetes mellitus: a case report. J Obstet Gynaecol Res. 2014 Nov;40(11):2158-61. doi: 10.1111/jog.12477. Epub 2014 Aug 28. PMID: 25164320.
25. Garnaud C, Fricker-Hidalgo H, Evengård B, Álvarez-Martínez MJ, Petersen E, Kortbeek LM, Robert-Gangneux F, Villena I, Costache C, Paul M, Meroni V, Guy E, Chiodini PL, Brenier-Pinchart MP, Pelloux H; under the auspices of the ESGCP of ESCMID. Toxoplasma gondii-specific IgG avidity testing in pregnant women. Clin Microbiol Infect. 2020 Sep;26(9):1155-1160. doi: 10.1016/j.cmi.2020.04.014.
26. Piao LX, Cheng JH, Aosai F, Zhao XD, Norose K, Jin XJ. Cellular immunepathogenesis in primary Toxoplasma gondii infection during pregnancy. Parasite Immunol. 2018 Sep;40(9):e12570. doi: 10.1111/pim.12570.
27. Picone O, Fuchs F, Benoist G, Binquet C, Kieffer F, Wallon M, Wehbe K, Mandelbrot L, Villena I. Toxoplasmosis screening during pregnancy in France: Opinion of an expert panel for the CNGOF. J Gynecol Obstet Hum Reprod. 2020 Sep;49(7): 101814. doi: 10.1016/j.jogoh.2020.101814.
28. Bailão LA, Osborne NG, Rizzi MC, Bonilla-Musoles F, Duarte G, Bailão TC. Ultrasound markers of fetal infection, Part 2: Bacterial, parasitic, and fungal infections. Ultrasound Q. 2006 Jun;22(2):137-51. doi: 10.1097/00013644-200606000-00026.
29. Codaccioni C, Picone O, Lambert V, Maurice P, Pomar L, Winer N, Guibaud L, Lavergne RA, Saliou AH, Quinio D, Benachi A, Noel C, Ville Y, Cuillier F, Pomares C, Ferret N, Filisetti D, Weingertner AS, Vequeau-Goua V, Cateau E, Benoist G, Wallon M, Dommergues M, Villena I, Mandelbrot L. Ultrasound features of fetal toxoplasmosis: A contemporary multicenter survey in 88 fetuses. Prenat Diagn. 2020 Dec;40(13): 1741-1752. doi: 10.1002/pd.5756.
30. Freeman K, Salt A, Prusa A, Malm G, Ferret N, Buffolano W, Schmidt D, Tan HK, Gilbert RE; European Multicentre Study on Congenital Toxoplasmosis. Association between congenital toxoplasmosis and parent-reported developmental outcomes, concerns, and impairments, in 3 year old children. BMC Pediatr. 2005 Jul 13;5:23. doi: 10.1186/1471-2431-5-23.

31. Dhombres F, Friszer S, Maurice P, Gonzales M, Kieffer F, Garel C, Jouannic JM. Prognosis of Fetal Parenchymal Cerebral Lesions without Ventriculomegaly in Congenital Toxoplasmosis Infection. Fetal Diagn Ther. 2017;41(1):8-14. doi: 10.1159/000445113.
32. Kieffer F, Wallon M, Garcia P, Thulliez P, Peyron F, Franck J. Risk factors for retinochoroiditis during the first 2 years of life in infants with treated congenital toxoplasmosis. Pediatr Infect Dis J. 2008 Jan;27(1):27-32. doi: 10.1097/INF.0b013 e318134286d.
33. Bastien P. Molecular diagnosis of toxoplasmosis. Trans R Soc Trop Med Hyg. 2002 Apr;96 Suppl 1:S205-15. doi: 10.1016/s0035-9203(02)90078-7.
34. Gilbert RE, Peckham CS. Congenital toxoplasmosis in the United Kingdom: to screen or not to screen? J Med Screen. 2002;9(3):135-41. doi: 10.1136/jms.9.3. 135.
35. Paquet C, Yudin MH. No. 285-Toxoplasmosis in Pregnancy: Prevention, Screening, and Treatment. J Obstet Gynaecol Can. 2018 Aug;40(8):e687-e693. doi: 10.1016/j.jogc.2018.05.036.
36. Practice bulletin no. 151: Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015 Jun;125(6):1510-1525. doi: 10.1097/ 01.AOG.0000466430.19823.53.
37. Wallon M, Peyron F, Cornu C, Vinault S, Abrahamowicz M, Kopp CB, Binquet C. Congenital toxoplasma infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. Clin Infect Dis. 2013 May;56(9): 1223-31. doi: 10.1093/cid/cit032.
38. Avelino MM, Amaral WN, Rodrigues IM, Rassi AR, Gomes MB, Costa TL, Castro AM. Congenital toxoplasmosis and prenatal care state programs. BMC Infect Dis. 2014 Jan 18;14:33. doi: 10.1186/1471-2334-14-33.
39. Gras L, Gilbert RE, Wallon M, Peyron F, Cortina-Borja M. Duration of the IgM response in women acquiring Toxoplasma gondii during pregnancy: implications for clinical practice and cross-sectional incidence studies. Epidemiol Infect. 2004 Jun;132(3):541-8. doi: 10.1017/s0950268803001948.
40. Liesenfeld O, Press C, Montoya JG, Gill R, Isaac-Renton JL, Hedman K, Remington JS. False-positive results in immuneglobulin M (IgM) toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. J Clin Microbiol. 1997 Jan;35(1):174-8. doi: 10.1128/jcm.35.1.174-178.1997.
41. de Ory F, Casas I, Domingo CJ, Echevarría J. Application of fluoroimmunoassay to the identification of low avidity specific IgG against pathogenic human viruses and Toxoplasma gondii. Clin Diagn Virol. 1995 May;3(4):323-32. doi: 10.1016/0928-0197(94)00045-v.
42. Cozon GJ, Ferrandiz J, Nebhi H, Wallon M, Peyron F. Estimation of the avidity of immunoglobulin G for routine diagnosis of chronic Toxoplasma gondii infection in pregnant women. Eur J Clin Microbiol Infect Dis. 1998 Jan;17(1):32-6. doi: 10.1007/BF01584360.
43. Lefevre-Pettazzoni M, Le Cam S, Wallon M, Peyron F. Delayed maturation of immunoglobulin G avidity: implication for the diagnosis of toxoplasmosis in pregnant women. Eur J Clin Microbiol Infect Dis. 2006 Nov;25(11):687-93. doi: 10.1007/s10096-006-0204-1.
44. Meroni V, Genco F, Tinelli C, Lanzarini P, Bollani L, Stronati M, Petersen E. Spiramycin treatment of Toxoplasma gondii infection in pregnant women impairs the production and the avidity maturation of T. gondii-specific immunoglobulin G antibodies. Clin Vaccine Immunol. 2009 Oct;16(10):1517-20. doi: 10.1128/CVI.00253-09.
45. Murat JB, L'Ollivier C, Fricker Hidalgo H, Franck J, Pelloux H, Piarroux R. Evaluation of the new Elecsys Toxo IgG avidity assay for toxoplasmosis and new insights into the interpretation of avidity results. Clin Vaccine Immunol. 2012 Nov;19(11):1838-43. doi: 10.1128/CVI.00333-12.
46. Gay-Andrieu F, Fricker-Hidalgo H, Sickinger E, Espern A, Brenier-Pinchart MP, Braun HB, Pelloux H. Comparative evaluation of the ARCHITECT Toxo IgG, IgM, and IgG Avidity assays for anti-Toxoplasma antibodies detection in pregnant women sera. Diagn Microbiol Infect Dis. 2009 Nov;65(3):279-87. doi: 10.1016/j.diagmicrobio.2009.07.013.
47. Fricker-Hidalgo H, Saddoux C, Suchel-Jambon AS, Romand S, Foussadier A, Pelloux H, Thulliez P. New Vidas assay for Toxoplasma-specific IgG avidity: evaluation on 603 sera. Diagn Microbiol Infect Dis. 2006 Oct;56(2):167-72. doi: 10.1016/j.diagmicrobio.2006.04.001.
48. Fricker-Hidalgo H, L'Ollivier C, Bosson C, Imbert S, Bailly S, Dard C, Piarroux R, Paris L, Pelloux H. Interpretation of the Elecsys Toxo IgG avidity results for very low and very high index: study on 741 sera with a determined date of toxoplasmosis. Eur J Clin Microbiol Infect Dis. 2017 May;36(5):847-852. doi: 10.1007/s10096-016-2870-y.
49. Villard O, Breit L, Cimon B, Franck J, Fricker-Hidalgo H, Godineau N, Houze S, Paris L, Pelloux H, Villena I, Candolfi E; French National Reference Center for Toxoplasmosis Network. Comparison of four commercially available avidity tests for Toxoplasma gondii-specific IgG antibodies. Clin Vaccine Immunol. 2013 Feb;20(2): 197-204. doi: 10.1128/CVI.00356-12.
50. Findal G, Stray-Pedersen B, Holter EK, Berge T, Jenum PA. Persistent Low Toxoplasma IgG Avidity Is Common in Pregnancy: Experience from Antenatal Testing in Norway. PLoS One. 2015 Dec 29;10(12):e0145519. doi: 10.1371/journal.pone.0145519.

51. Montoya JG, Huffman HB, Remington JS. Evaluation of the immunoglobulin G avidity test for diagnosis of toxoplasmic lymphadenopathy. J Clin Microbiol. 2004 Oct;42(10):4627-31. doi: 10.1128/JCM.42.10.4627-4631.2004.
52. Flori P, Tardy L, Patural H, Bellete B, Varlet MN, Hafid J, Raberin H, Sung RT. Reliability of immunoglobulin G antitoxoplasma avidity test and effects of treatment on avidity indexes of infants and pregnant women. Clin Diagn Lab Immunol. 2004 Jul;11(4):669-74. doi: 10.1128/ CDLI.11.4.669-674.2004.
53. Candolfi E, Pastor R, Huber R, Filisetti D, Villard O. IgG avidity assay firms up the diagnosis of acute toxoplasmosis on the first serum sample in immunocompetent pregnant women. Diagn Microbiol Infect Dis. 2007 May;58(1):83-8. doi: 10.1016/j. diagmicrobio.2006.12.010.
54. Garabedian C, Le Goarant J, Delhaes L, Rouland V, Vaast P, Valat AS, Subtil D, Houfflin-Debarge V. Séroconversion toxoplasmique périconceptionnelle : à propos de 79 cas [Periconceptional toxo-plasmic seroconversion: about 79 cases]. J Gynecol Obstet Biol Reprod (Paris). 2012 Oct;41(6):546-52. French. doi: 10.1016/j. jgyn.2012.03.006.
55. Olariu TR, Blackburn BG, Press C, Talucod J, Remington JS, Montoya JG. Role of *Toxoplasma* IgA as Part of a Reference Panel for the Diagnosis of Acute Toxoplasmosis during Pregnancy. J Clin Microbiol. 2019 Jan 30;57(2):e01357-18. doi: 10.1128/JCM.01357-18.
56. Lachaud L, Calas O, Picot MC, Albaba S, Bourgeois N, Pratlong F. Value of 2 IgG avidity commercial tests used alone or in association to date toxoplasmosis contamination. Diagn Microbiol Infect Dis. 2009 Jul;64(3):267-74. doi: 10.1016/j. diagmicrobio. 2009.02.014.
57. Smets A, Fauchier T, Michel G, Marty P, Pomares C. Comparison of Toxoplasma gondii IgG avidity Architect and Vidas assays with the estimated date of infection in pregnant women. Parasite. 2016;23:45. doi: 10.1051/ parasite/2016056.
58. Boquel F, Monpierre L, Imbert S, Touafek F, Courtin R, Piarroux R, Paris L. Interpretation of very low avidity indices acquired with the Liaison XL Toxo IgG avidity assay in dating toxoplasmosis infection. Eur J Clin Microbiol Infect Dis. 2019 Feb;38(2):253-257. doi: 10.1007/ s10096-018-3421-5.
59. de Oliveira Azevedo CT, do Brasil PE, Guida L, Lopes Moreira ME. Performance of Polymerase Chain Reaction Analysis of the Amniotic Fluid of Pregnant Women for Diagnosis of Congenital Toxoplasmosis: A Systematic Review and Meta-Analysis. PLoS One. 2016 Apr 7;11(4):e0149938. doi: 10.1371/journal.pone. 0149938.
60. Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. Clin Infect Dis. 2008 Aug 15;47(4):554-66. doi: 10.1086/ 590149.
61. Neville AJ, Zach SJ, Wang X, Larson JJ, Judge AK, Davis LA, Vennerstrom JL, Davis PH. Clinically Available Medicines Demonstrating Anti-Toxoplasma Activity. Antimicrob Agents Chemother. 2015 Dec;59(12):7161-9. doi: 10.1128/AAC. 02009-15.
62. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of Toxoplasmosis: Historical Perspective, Animal Models, and Current Clinical Practice. Clin Microbiol Rev. 2018 Sep 12;31(4): e00057-17. doi: 10.1128/CMR.00057-17.
63. Peyron F, Wallon M, Liou C, Garner P. Treatments for toxoplasmosis in pregnancy. Cochrane Database Syst Rev. 2000; 1999(2):CD001684. doi: 10.1002/ 14651858.CD001684.
64. Wallon M, Kieffer F, Huissoud C, Peyron F. Cesarean delivery or induction of labor does not prevent vertical transmission of toxoplasmosis in late pregnancy. Int J Gynaecol Obstet. 2015 May;129(2):176-7. doi: 10.1016/ j.ijgo.2014.10.026.
65. Cook AJ, Gilbert RE, Buffolano W, Zufferey J, Petersen E, Jenum PA, Foulon W, Semprini AE, Dunn DT. Sources of toxoplasma infection in pregnant women: European multicentre case-control study. European Research Network on Congenital Toxoplasmosis. BMJ. 2000 Jul 15;321(7254):142-7. doi: 10.1136/bmj. 321.7254.142.
66. Kapperud G, Jenum PA, Stray-Pedersen B, Melby KK, Eskild A, Eng J. Risk factors for Toxoplasma gondii infection in pregnancy. Results of a prospective case-control study in Norway. Am J Epidemiol. 1996 Aug 15;144(4):405-12. doi: 10.1093/oxfordjournals. aje.a008942.
67. Baril L, Ancelle T, Goulet V, Thulliez P, Tirard-Fleury V, Carme B. Risk factors for Toxoplasma infection in pregnancy: a case-control study in France. Scand J Infect Dis. 1999;31(3):305-9. doi: 10.1080/ 00365549950163626.
68. Bahia-Oliveira LM, Jones JL, Azevedo-Silva J, Alves CC, Oréfice F, Addiss DG. Highly endemic, waterborne toxoplasmosis in north Rio de Janeiro state, Brazil. Emerg Infect Dis. 2003 Jan;9(1):55-62. doi: 10.3201/ eid0901.020160.
69. Dubey JP. Strategies to reduce transmission of Toxoplasma gondii to animals and humans. Vet Parasitol. 1996 Aug; 64(1-2):65-70. doi: 10.1016/0304-4017(96) 00961-2.
70. Opsteegh M, Kortbeek TM, Havelaar AH, van der Giessen JW. Intervention strategies to reduce human Toxoplasma gondii disease burden. Clin Infect Dis. 2015 Jan 1;60(1):101-7. doi: 10.1093/cid/ciu721.

71. Warnekulasuriya MR, Johnson JD, Holliman RE. Detection of Toxoplasma gondii in cured meats. Int J Food Microbiol. 1998 Dec 22;45(3):211-5. doi: 10.1016/s0168-1605(98)00158-5.
72. Buffolano W, Gilbert RE, Holland FJ, Fratta D, Palumbo F, Ades AE. Risk factors for recent toxoplasma infection in pregnant women in Naples. Epidemiol Infect. 1996 Jun;116(3):347-51. doi: 10.1017/ s0950268800052675.
73. Paquet C, Yudin MH; Society of Obstetricians and Gynaecologists of Canada. Toxoplasmosis in pregnancy: prevention, screening, and treatment. J Obstet Gynaecol Can. 2013 Jan;35(1):78-81. English, French. doi: 10.1016/s1701-2163(15)31053-7.
74. Guy EC, Joynson DH. Potential of the polymerase chain reaction in the diagnosis of active Toxoplasma infection by detection of parasite in blood. J Infect Dis. 1995 Jul;172(1):319-22. doi: 10.1093/infdis/172.1.319.
75. Kur J, Holec-Gasior L, Hiszczyñska-Sawicka E. Current status of toxoplasmosis vaccine development. Expert Rev Vaccines. 2009 Jun;8(6):791-808. doi: 10.1586/erv.09.27.
76. Liu Q, Singla LD, Zhou H. Vaccines against Toxoplasma gondii: status, challenges and future directions. Hum Vaccin Immunother. 2012 Sep;8(9):1305-8. doi: 10.4161/hv.21006.