



## MEDICAL, LEGAL AND ETHICAL IMPLICATIONS OF TOXOPLASMOSIS DIAGNOSIS DURING PREGNANCY

Bujor-Moraru Mihaela, Ispas C.A.

Caritas Obstetrics Gynecology Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

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**Abstract.** Toxoplasmosis diagnosis in a pregnant woman brings along a series of medical, legal and also ethical implications regarding the consequent evolution of the pregnancy and the decisions which need to be taken. Starting with the medical implications, represented by the possible fetal affectation, the prenatal diagnosis maneuvers and procedures, the therapy administered throughout the pregnancy, we continue with the legal implications, represented by the necessity and the possibility to test the pregnant woman for toxoplasmosis and by the consequences of an infected mother giving birth to a malformed fetus and we conclude with a series of ethical implications of diagnosing toxoplasmosis during pregnancy.

**Keywords:** *Toxoplasma gondii*, toxoplasmosis during pregnancy, toxoplasmosis during pregnancy legal and ethical

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### Introduction

This article presents certain general aspects of toxoplasmosis during pregnancy, together with data regarding epidemiology, diagnosis and treatment. The prenatal diagnosis of *Toxoplasma gondii* infection, followed by prenatal therapy, would considerably reduce the severity and the frequency of congenital infections. In order to prevent congenital infections, testing for *Toxoplasma gondii* should be introduced as screening test for all women who wish to become pregnant or who are already pregnant.

### Epidemiology of *Toxoplasma gondii* infection

The infection can be transmitted through digestive route, through direct contact with the feces of an infected cat, it can be airborne, transplacental, or transmitted through blood or organ transplant [1].

Acquired toxoplasmosis usually occurs after ingesting food contaminated with sporulated oocysts [1], ingesting insufficiently cooked meat containing tissue cysts, or by direct contact with soil or other materials contaminated with cat feces containing viable oocysts [1]. There have also been reported very few cases of infection following transfusions, contaminated organ transplants, and a laboratory accident.

*Toxoplasma* seroprevalence appears to increase with ageing, with reports of considerable variations in different geographic areas [3]. The seroprevalence in the United States of America was reported to be between 3% in Denver and 35% in Miami, and 10 and 14% in Boston and respectively Palo Alto, California. The seroprevalence of *Toxoplasma* in Africa, Europe and Latin America is considerably higher, with values varying between 21% (London), 72% (Paris), 23% (Zambia), 81% (Centrafrican Republic), 59% (Santiago de Chile) and 65% (Belo Horizonte, Brazil) [3].

The incidence of toxoplasmosis varies widely throughout the world, from 0% in certain areas in Alaska and Canada to 94% in Guatemala and Costa Rica [3]. Given the fact that the percentage of toxo-

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M. Bujor-Moraru, Assist. Lect., MD, PhD student  
e-mail: mihaelabujormoraru@yahoo.com

plasmosis seronegative pregnant women seems to be increasing, a good monitoring of this investigation during pregnancy is mandatory, because of the high risk of primary infection during pregnancy.

The vast majority of the cases of congenital transmission occurred because of a primary *Toxoplasma gondii* infection during pregnancy.

Most cases of primary infection in immunocompetent hosts are asymptomatic or nonspecific, and as a consequence they are not investigated. In other cases though, the patient may present mononucleosis-like symptoms [4].

Per se manifestations of toxoplasmosis in a pregnant woman, especially when associated with lymphadenopathy and tiredness without fever, must lead to an epidemiological investigation for acute acquired toxoplasmosis [5]. In the geographical areas in which the seroprevalence is high (in France and some Central America countries, for example), the testing threshold is usually lower.

The risk of transplacental transmission is highest when the mother is infected late during the gestation period. But the neonatal symptomatic infection frequency is lowest in these children. *Toxoplasma gondii* infection of clinical significance occurs during the intrauterine life, by transplacental passage of the parasite. When the mother acquires the infection during pregnancy, this usually leads to bloodborne dissemination at the placenta level. In this case, the sequence of events is the following: the primary infection of the mother, parasitemia, placenta infection and hematogenous propagation to the fetus.

The transplacental transmission of the parasite seems to also be influenced by other factors: the blood flow passing the placenta, the intensity of the parasitemia, the virulence of the *T gondii* stem, and the genetic susceptibility of the organism.

According to the literature data, the transmission rate of the infection to the conception product during the maternal primary infection is about 40% [5]. In other cases, the infestation of the pregnant woman is followed by the production of antibodies and the activation of the cellular immune mechanisms before transplacental invasion, thus the fetus remains normal and will be born healthy.

Although the congenital infection risk for children born from mothers who were infected early during the gestation period is considerably lower, the frequency of neonatal symptomatology is higher [1,6].

### **Congenital Toxoplasmosis**

Although there are certain clinical signs that may be present in children with symptomatic congenital toxoplasmosis, the capacity to diagnose this condition based on clinical exam is often challenging. The

spectrum of manifestations of this disease may vary widely and it may mimic other transplacental or perinatally acquired infections. Also, most children who were congenitally infected (around 70-90%) are asymptomatic at birth [1,5,6,7]. Most of these children will not develop signs or symptoms until months or years later, when they present clinically significant scars, most frequently affecting the eyes or the brain [6, 8]. In most cases the disease cannot be identified, these scars being useful in a late diagnosis of the infectious disease [1].

Almost 20% of the newborns mentioned above have had clinically silent ocular or brain conditions [1]. The late onset disease appears most frequently in premature newborns, usually in the first 3 months of life. Ocular toxoplasmosis can be reactivated months or years later in immunocompetent patients, and also in immunocompromised patients. However, there is no way of telling with certainty which of the children will develop late complications [5]. For this reason an early diagnosis of congenital toxoplasmosis is crucial, together with the onset of the specific treatment in order to reduce or limit the complications [9].

A newborn may present a symptomatic disease, with the classic triad of hydrocephalus (secondary to the periapical stenosis), intracranial calcifications and chorioretinitis (usually bilateral). This triad appears in only a minority of the symptomatic patients [4, 10]. The clinical manifestations are usually not specific and they include one or more of the following manifestations, which appear in more than 50% of the affected children: diffuse maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly, jaundice, ocular diseases (cataract, microphthalmia, optic atrophy and chorioretinitis), abnormal spinal fluid, convulsions, fever and anemia [1, 5].

Congenital toxoplasmosis occurs when the mother gets infected or when there is a reactivation of an older infection during pregnancy. The severity of the affection is influenced by the type of infection (primary infection or reactivation), by the age of the pregnancy, but also by the competence of the maternal immune system [7]. Despite the mother's possibly asymptomatic form of disease, an infection occurring during the first trimester of pregnancy may determine spontaneous abortion, the death of the fetus at birth or important neurological and ophthalmic lesions, hydrocephalus or microcephalus, intracranial calcifications and chronic chorioretinitis [3]. In the last trimester, the infection can determine jaundice of the newborn, hepatosplenomegaly, psychomotor retard or ocular manifestations (strabismus, blindness, cataract) and liver manifestations, sometimes leading to death [14].

## Diagnosis of the congenital infection

Serologic screening tests are currently used in many European countries for detecting congenital and perinatal infections [8]. French guidelines recommend monthly testing of pregnant women throughout the whole pregnancy in order to detect seroconversion.

In the United States, screening is recommended only in case of suggestive findings on the ultrasound prenatal tests: hydrocephalus, intracranial calcifications, microcephalus, fetus growth restrictions, ascites or hepatosplenomegaly [9]. The post-conception onset of the primary infection of the mother must be confirmed prior to any attempt to diagnose the infection in utero. Although many clinical laboratories are equipped for a preliminary diagnosis of the primary infection based on the determination of the existence of *T gondii* IgG and IgM antibodies, these results must be confirmed by a reference laboratory before attempting any invasive procedure.

Considering the efficacy and safety of amniocentesis, polymerase chain reaction (PCR) and of the testing of the amniotic fluid for *T gondii*, these were labeled as methods of choice for the in utero diagnosis of the infection. Cordocentesis (transabdominal fetal blood absorption performed through introducing a sterile needle into the umbilical vein) has also been successfully used for the in utero infection diagnosis and it can be used as alternative diagnosis procedure, if needed [1]. A fetal loss rate of 0.3 out of 1000 has been reported for this method [1]. We emphasize the fact that even though the fetus proves not to be infected, the risk for the newborn must be reevaluated during the neonatal period because the transplacental infection may occur even in the late stages of pregnancy.

## Treatment of the congenital infection

The medical treatment of the congenital *T gondii* infection is comprised of an association of spiramycin or pyrimethamine and sulfadiazine, administered prenatally and postnatally for 6 to 12 months. This therapy has been proved to be efficient both for the decrease of the transplacental transmission rate of the parasite and for the decrease of its effects on the fetus and of the later sequelae. The postnatal treatment (both in the symptomatic and the asymptomatic forms) may lead to the correction of the intellectual function, regression of retinal lesions, reduction of seizures and prevention of hearing impairment. The option of therapeutic abortion must be considered when the primary infection of the mother occurs during the first trimester of pregnancy and when there are definite signs of severe illness of the fetus [1,5].

The majority of the pregnant women in an early

stage of pregnancy which are detected with positive toxoplasma IgM antibodies choose to end the pregnancy, its continuation representing a major risk for fetal malformations [7].

The prophylaxis measures for toxoplasmosis during pregnancy range from hygiene measures (washing hands, etc.) and appropriate thermal preparation of the ingested meat to a series of methods of following the dynamics of the antibodies in order to observe the moment of seroconversion. For this reason, for a seronegative pregnant woman, a monthly reevaluation of the anti-toxoplasma antibodies is recommended [10].

## Ethical and legal aspects of the *Toxoplasma gondii* infection during pregnancy

The interruption of the pregnancy for a woman with positive toxoplasmosis IgM antibodies cannot be performed after 14 weeks of gestation, because the Romanian legislation does not recognize this as a legal reason for abortion [11]. For this reason, the evaluation of the titer of IgM antibodies after the 14<sup>th</sup> week of gestation seems useless, since the legal period for the abortion is overdue, but it is still performed in order to diagnose and impose a treatment, even though the mother is forced, according to the law [11], to accept giving birth to a child with a great potential of being severely malformed. The small C-section can be performed only if there is evidence that the pregnancy may pose a threat to the mother's life, but these situations are not directly connected to the presence or absence of the *T gondii* infection, but rather to certain obstetrical conditions (placenta praevia with hemorrhaging, pregnancy induced arterial hypertension not responding to treatment) or other maternal conditions (hepatorenal failure, cardiac conditions).

Another rather legal issue is represented by the fact that in Romania, in theory, healthcare is free during pregnancy, and the usual tests performed during pregnancy should be free of charge. Basically, the absence of this test from the list of mandatory tests during pregnancy should be regarded as a safeguard factor for the situations in which this test was not prescribed by the obstetrician when following a normal pregnancy [12]. It is obvious that in this situation a good clinical practice guideline is needed for establishing when this test should be performed during pregnancy, and at which gestation age.

The FIGO (International Federation of Gynecology and Obstetrics) Committee for the Study of Ethical Aspects of Human Reproduction and Women's Health has developed a series of recommendations regarding the interruption of a pregnancy after an abnormal result of a prenatal

diagnostic exam. As such, a first step is represented by the recommendation of performing prenatal diagnostic exams only to those patients who plan to abort a pregnancy if the results of the exam are abnormal [13]. There are families which for personal, religious or other reasons refuse ab initio the idea of an abortion, even if the result of the pregnancy may be a seriously malformed fetus, incompatible with life [10]. But even for these families, the physician has to present the prenatal tests which should be performed in each individual case.

In the eventuality of abnormal results, the physician must inform the family correctly and completely about the risks represented by the continuation of the pregnancy, in order to obtain a genuine informed consent if the decision is to perform an abortion. The physician has to be careful not to convince the family that the abortion is necessary, his professional duty being that of exposing the risks and medical implications of an eventual congenital toxoplasmosis. Also, an abortion is indicated when there are elements that confirm the existence of a fetal malformation determined by the respective pathogen, regardless of the age of the pregnancy, but considering each country's law. If a decision in favor of the abortion is made and a uterine curettage is performed or the abortion is induced by other means, it is indicated that the parents see, if they are up to it, the malformed conception product, and that the latter is sent for a histopathological confirmation of the suspected malformations [12]. The parents should receive, if possible, psychological counseling to help them cope with such a traumatic event [13].

These ethical implications of a pregnancy abortion should be taken into account each time a fetal malformation is suspected.

We have to mention that in the situation in which the family refuses to interrupt a pregnancy which will have as result a plurimalformed fetus, it is both ethically and legally mandatory to provide the best medical care for the mother during labor and for the surviving malformed fetus [13].

The above mentioned legal implications may lead to some possible accusations of malpractice addressed to the Medical Council, which will study the case, will discuss it and then will take the appropriate measures in order to solve the complaint. In some cases it may even be taken to court, but the Medical Council is the institution which has to decide whether a medical act constitutes an infringement of the good clinical practice. Also, all authorized institutions should decide in favor of the introduction of zoonosis testing as a screening test for pregnant women, and the prevention of these diseases should constitute an important aspect of medical practice [14].

## Conclusions

*Toxoplasma gondii* is one of the most frequent parasite infections in the whole world, and the severity of the disease caused by this parasite has determined the medical system to take the appropriate measures in order to prevent these consequences.

It is necessary to perform the monitoring of the seronegative pregnant women every 4-6 weeks, in order to establish the exact moment of an eventual seroconversion (IgA, IgM, IgE), and of those with chronic infection every 8-10 weeks, and especially monthly during the last trimester (IgE and IgG).

Monitoring a pregnant woman with toxoplasmosis requires a multidisciplinary approach: obstetrics, parasitology, neonatology, pediatrics, ophthalmology, general physician.

A favorable evolution and outcome depend on the early diagnosis and onset of an adequate etiological and symptomatic treatment.

An important issue is represented by the prevention of *T gondii* infection during pregnancy and subsequently of congenital toxoplasmosis, because it would be the most inexpensive way to solve this matter. A very important goal would be a proper education regarding the sources of infection and a serologic screening throughout the pregnancy because of the serious problems caused by the *T gondii* infection during pregnancy: spontaneous abortion or premature birth, the necessity to perform an abortion or the birth of malformed fetuses.

The investigation and treatment of toxoplasmosis based on guidelines and/or medical protocols in nurseries should be taken into account, together with their implementation in nation-wide screening and treatment programs.

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