CASE REPORT

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Pregnancy with seropositive toxoplasmosis: A case report

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ABSTRACT

Introduction: Toxoplasmosis is present in every country and seropositive rates vary between regions from less than 10% to more than 90%. Toxoplasmosis in pregnancy can result in severe sequelae to the fetus. Primary infection in pregnancy may cause spontaneous abortion or fetal death in utero. Congenital ocular and neurological abnormalities may also occur. We present a case involving toxoplasmosis infection in early pregnancy and an overview of the management and the clinical outcomes for both mother and fetus.

Case report: A 26-year-old pregnant woman (G1P0A0) showed a high concentration of IgG anti-toxoplasmosis in early pregnancy with a concentration of 1200. Throughout the pregnancy, an increase in the concentration of IgG anti-toxoplasma was found. At 14 weeks gestation, concentration increased four-fold to 9068. During the ultrasound observation no hydrocephalus, ocular, and neurological abnormalities were found. Amniocentesis was performed for PCR examination and the result turned out negative. The patient was given spiramycin 1 gram daily for the remaining of her pregnancy. At 40 weeks gestation, the patient gave birth vaginally to a healthy term 3700 grams baby boy. There were no signs of major anomalies found in the baby.

Conclusions: Diagnosis and screening of toxoplasmosis require proper understanding of serological examination, as well as the specificity and sensitivity of the diagnostic tools. Ultrasound monitoring for the detection of congenital toxoplasmosis can also help with diagnosis.

Keywords: Toxoplasmosis, pregnancy, serology, diagnosis.

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INTRODUCTION

Toxoplasmosis is found throughout the world and the seropositive rate varies between regions from less than 10% to more than 90%. The causative agent for toxoplasmosis is Toxoplasma gondii which has a complex life cycle. Toxoplasmosis in pregnancy can result in severe sequelae in the fetus. Primary infection in pregnancy can cause spontaneous abortion or intrauterine fetal death, as well as ocular and neurological abnormalities.[1]

In 2013 World Health Organization (WHO) issued a bulletin regarding the global burden of toxoplasmosis in pregnancy. It was explained that the seroprevalence rate in pregnancy is estimated to be around 15.4-24.3%. Globally, the incidence of acute primary infection in pregnancy ranges from 1-8 per 1000 pregnancies. It was reported in the United States that the seroprevalence rate in women of reproductive age (19-45 years) reached 9% in 2009-2010 and the annual cost of treating toxoplasmosis was estimated to be US $ 7.7 billion.[1]

A higher seroprevalence was found in tropical areas, especially in areas exposed to contaminated soil, having a consumption habit of undercooked meat, and unfiltered water. For the Southeast Asian region, the rates may be higher which was reported to reach around 13%. In another study, seroprevalence ranges from 8 to 37% in India and 28% in Thailand. Pappas et al. examined seroprevalence rates in Asia, they found relatively higher scores in areas such as Indonesia and Malaysia and relatively lower rates in Thailand and Vietnam. Indonesia is reported to have a reasonably high seroprevalence rate of 36.9%.[1–3] Meanwhile, data in Bali Province is very limited. There is only one study conducted in Gianyar province where 240 serum samples were collected and a seroprevalence of 56.7% was reported. The high number was suspected due to the behavior of eating undercooked food. Although this value was not in the population of pregnant women, it can be a basis for thinking that toxoplasmosis do exist in Balinese society.[4]

The data above proved that toxoplasmosis is present in all countries and is a health problem that must be solved because of the enormous risk of congenital abnormalities that accompanies it. The fetal infection results from transplacental tachyzoite transmission at the time of primary infection. Transmission most likely occurs in the parasitemia phase several days after the maternal infection and several days before the maternal serological response. Mother-to-child transmission occurs only when the primary infection occurs

during pregnancy and the risk of transmission increases with increasing gestational age. Overall, about one-third of affected mothers will give birth to a child with toxoplasmosis. Most children born with toxoplasmosis will grow up without defects. However, about 4% will die or have neurological or visual disturbances that will appear later in the first year of life.[5]

Toxoplasmosis infection in pregnancy is asymptomatic and can only be detected by serological tests. Providing maternal antibiotic treatment can help reduce the risk of fetal infection. Therefore, it is essential to know whether fetal toxoplasmosis infection occurs during pregnancy.[6] Serologic tests for IgG and IgM antibodies are often used as the first step in making the diagnosis. The diagnostic challenge with serologic testing is to differentiate between primary infection and chronic infection. Sometimes the results of IgG and IgM tests are difficult to interpret. Some guidelines even recommend that the results need to be consulted further with an expert to confirm the diagnosis or to be sent to a reference laboratory. It is necessary to carry out other supporting examinations to help make the diagnosis.

In confirming the diagnosis, it is critical to determine whether there has been a transplacental transmission that could lead to fetal infection and to establish the timing of this fetal infection. By establishing the diagnosis of fetal infection, proper management can be carried out. A negative PCR result does not negate the possibility of mother-to-child transmission. There is also inconsistent evidence on whether or not pyrimethamine-sulfadiazine is needed.

CASE PRESENTATION

A 26-year-old woman, referred to Sanglah Hospital Denpasar with positive results of IgG and IgM anti-toxoplasmosis. IgG anti-toxoplasmosis titer was 1200, taken when she was 7 weeks pregnant. Physical examination and ultrasound revealed no abnormalities. The patient was suspected of having toxoplasmosis infection and spiramycin therapy was initiated. The patient was instructed to consume 1 gram of spiramycin three times daily and 400 micrograms of folic acid supplementation daily. She was scheduled for a visit in the following month.

At 14 weeks gestation, ultrasound findings were not indicative of toxoplasmosis infection. No major congenital abnormalities were found on the ultrasound. Subsequent serologic tests found a four-fold increase in IgG anti-toxoplasmosis titer, 9068. While the IgM-anti-toxoplasmosis remained positive, however her avidity was high (Table 1). These findings made it necessary to perform amniocentesis in order to confirm the diagnosis of fetal infection.

At 18 weeks gestation, a repeat scan was performed. We did not find the usual manifestations of toxoplasmosis such as chorioretinitis, intracranial calcification, and hydrocephalus. The lenses were clear, no visible enlargement of the liver, and no placentomegaly was found (Figure 1).

Table 1 Serial serological examination

Date and gestational age	Anti-toxoplasma Ig M	Anti-toxoplasma Ig G	Avidity	PCR Toxoplasmosis
20/01/18 (7 weeks 6 days)	Positive	Positive, concentration 1200		
08/03/18 (14 weeks 4 days)	Positive, concentration 62	Positive, concentration 9068	High avidity	
09/04/18 (19 weeks 1 days)				Negative
12/04/18 (19 weeks 4 days)	Positive, concentration 7.62	Positive, concentration 886		
25/05/18 (25 weeks 5 days)		Positive, concentration 846		
23/6/18 (29 weeks 6 days)		Positive, concentration 651		
25/07/18 (34 weeks 3 days)		Positive, concentration 566		
08/08/18 (36 weeks 3 days)	Positive	Positive, concentration 590		

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Table 2 The difference in sensitivity and specificity of PCR on placenta, umbilical cord, and amniotic fluid[9]

Location	Sensitivity (%)	Specificity (%)
Placenta	99	52
Umbilical cord	91	53
Amniotic fluid	91	99.5

Table 3 Sensitivity, Specificity, Positive and Negative Predictive Value of PCR Analysis Based on The Timing of Maternal Infection[11]

	First Trimester	Second Trimester	Third Trimester	Total
Sensitivity	75 (19-99)	97 (83-99.9)	88 (67-98.5)	92.2 (81-98)
Specificity	100 (97-100)	100 (95.4-100)	100 (66.4-100)	100 (98-100)
Positive predictive value	100 (29.2-100)	100 (88.1-100)	100 (78.2-100)	100 (92.5-100)
Negative predictive value	99 (96-99.9)	99 (93-99.9)	82 (48-98)	98.1 (95-99.5)

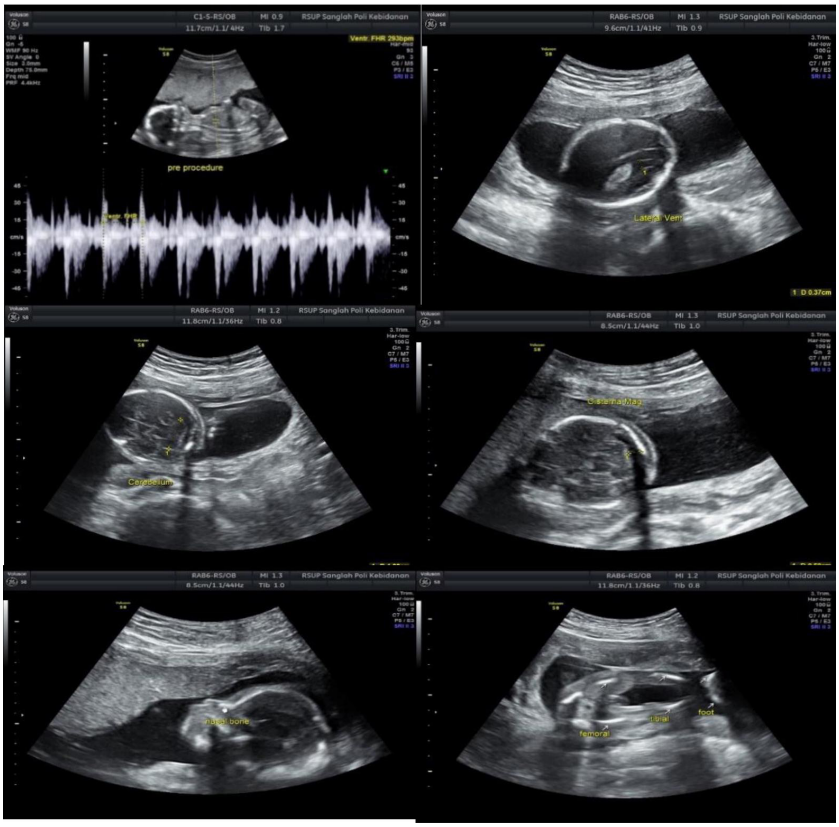

Figure 1 The ultrasound results at 18 weeks of pregnancy showed no signs of toxoplasmosis such as ventriculomegaly, ascites, temporal lobe calcification, hepatic calcification, and ascites

Amniocentesis was carried out and the result turned out to be negative (Table 1). It was decided to continue her spiramycin therapy.

We continued to monitor her serologic titer and a regular monthly scan was performed. During her control at 28 weeks gestation, no significant findings were found and the growth was adequate. Her titer showed a downward trend, IgG titer decreased to 846 (Table 1). At 40 weeks gestation patient delivered a healthy 3700 grams male infant with Apgar scores of 8 and 9 at 1 and 5 minutes respectively. No major congenital abnormalities were found in the baby. Four days after delivery, serologic testings were performed on the baby. Results were negative for IgM anti-toxoplasmosis and IgG titer was 486. During monitoring, the baby developed well and had no correlating symptoms of congenital toxoplasmosis. At 1 year of age, we repeated his serologic testings; both IgG and IgM anti-toxoplasmosis were negative.

DISCUSSION

Pathogenesis of toxoplasmosis in pregnancy

Toxoplasmosis infection is one of the most common parasitic infections in humans. It poses a great challenge when present in pregnancy as it may cause major ocular and neurological abnormalities in the infants, as well as intrauterine death and abortion.

The placenta serves to prevent infectious agents from entering the fetal compartment, especially in the early trimester of pregnancy compared to the final trimester. In primary infection, these parasites will pass through the intestinal barrier and invade the monocyte cells attached to the lamina propria, making it easier for the parasites to spread through the bloodstream to all organs including the placenta. Infection of the placental tissue can produce placentitis and can lead to infection of trophoblast cells located close to the fetal compartment.

T. gondii can invade and multiply in trophoblast cells, but the mechanism for failure of fetal protection against infection is still unclear and there are several hypotheses put forward against this mechanism. An efficient immune response against toxoplasma requires the Th-1 cytokine pathway which involves IFN-γ, the environment around the placenta which is rich in IL-10 and transforming growth factor (TGF) β-1 and enhanced Th-2 immune response to ensure maternal-tolerance that can facilitate infection of the placental tissue.[7]

Cytokines that play an essential role in this immune response are IFN-γ. In vitro, IFN-γ upregulated the expression of the intracellular adhesion molecule (ICAM)-1 adhesin on the surface of trophoblast cells and contributed to the increased adhesion of monocyte cells infected by these parasites. Also, ICAM-1 was induced during placentitis and directly assisted the transepithelial migration of parasites via MIC-2. The infected trophoblast cells will lose the ability to apoptosis, wherein the

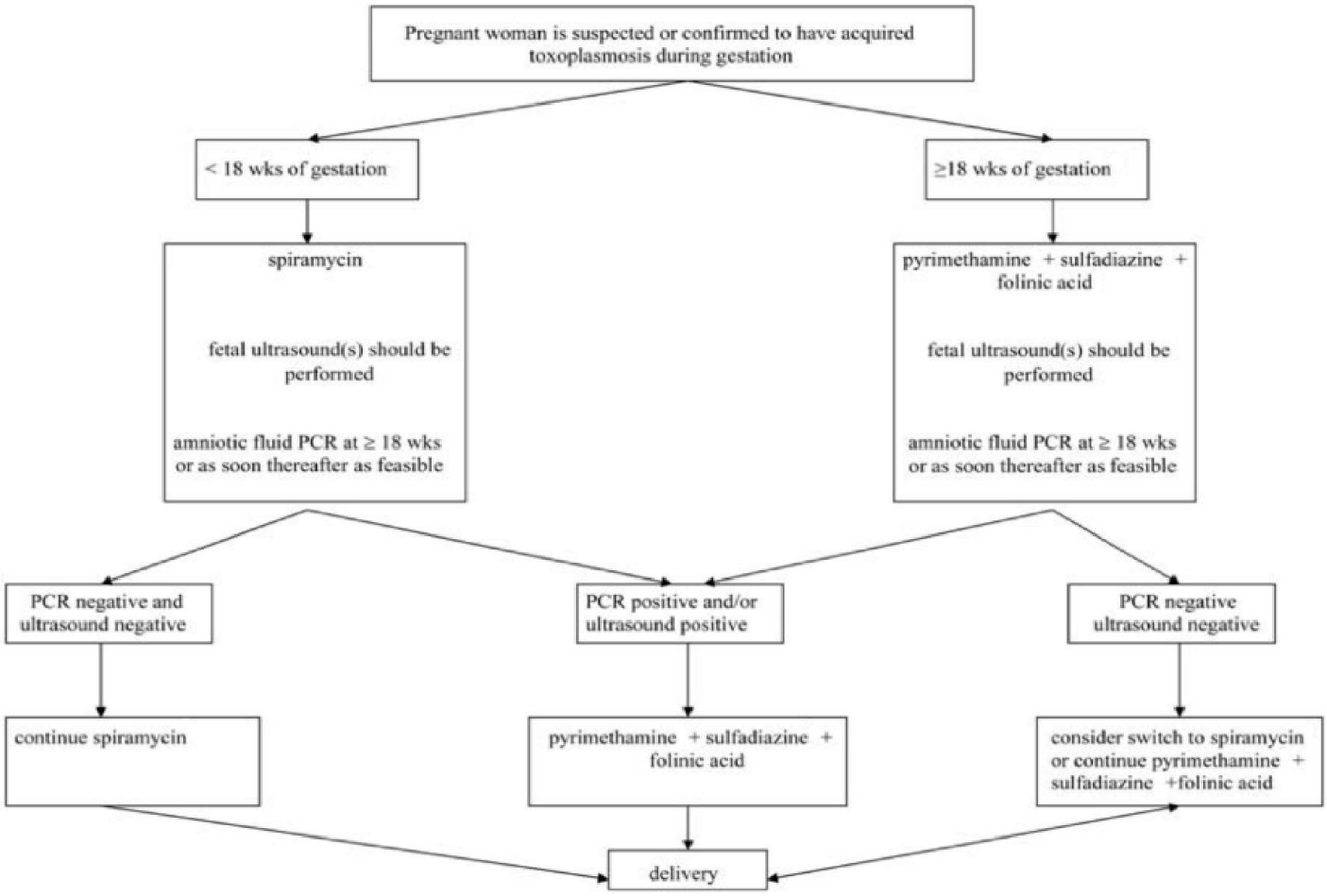

Figure 2 Approach for pregnant women who are suspected or confirmed to have toxoplasmosis acquired during gestation[13]

parasites will remain in the placental tissue. This is also supported by the strong expression of human leukocyte antigen (HLA)-G on trophoblast cells which inhibits cell lysis and suppresses the response of T-cytotoxic cells to the fetus. Persistent parasites in the placental tissue will be the source of congenital infection.[7]

In an infected placenta, placentitis will occur which can lead to the thickening and enlargement of placenta. During antenatal care, we did not find thickening of the placenta or placentomegaly. In the postpartum evaluation, there were no macroscopic abnormalities in the placenta.[8]

Intrauterine diagnosis of fetal infection

A positive IgM antibody signifies an acute infection. However it can still be found in the bloodstream from 1 week to 18 months after tachyzoite infection, while IgG antibody appears 1 to 2 months after initial infection. Both of these antibodies may overlap which make it challenging in determining the timing of the infection. Another tool is by performing IgG avidity test in which a higher avidity will be observed with longer time passed since the exposure. In this case, the patient had both positive IgG and IgM anti-toxoplasmosis antibodies which posed the question of whether she had an ongoing fetal infection. We performed ELISA IgG avidity test and the result was high which meant that her primary infection may occur 3 months prior. Since we performed this on her 14th week of pregnancy, a further investigation was needed to confirm whether the baby was infected. We decided to perform polymerase chain reaction on the amniotic fluid as the gold standard. Table 2 explains the difference in sensitivity and specificity between placenta, umbilical cord, and amniotic fluid (Table 3).

In interpreting PCR result, clinicians must understand its limitation. Amniotic fluid has the highest specificity of 99.5% and sensitivity of 91%. While the placenta and umbilical cord remains lower (Table 3). Therefore, a PCR of amniotic fluid done at 16 weeks gestation and above remains the gold standard in diagnosing intrauterine toxoplasmosis infection.[10]

Amniocentesis for the identification of T. gondii should not be carried out below 18 weeks of gestation as it carries a high false-positive value. A study done in Lyon France examined amniotic fluid PCR

screenings done in 3 centers. The study calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) on each trimester when the maternal infection occurred. PCR was carried out on 261 samples and they obtained a NPV of 98.1% and PPV of 100% (Table 3).[9,11]

In this patient her PCR test was carried out during her second trimester and the result was negative. With NPV of 99% for this trimester, there was a probability of 99% the baby did not have the infection. However, 1% possibility still remained that the infection could have occurred. Based on this result, we continued to monitor her during pregnancy and to continue her spiramycin medication. Furthermore, it is still necessary to monitor the new born baby for a 1-year post partum.

Management of toxoplasmosis in pregnancy

The appropriate management should be given to pregnant women who are suspected of having toxoplasma infection during pregnancy, either symptomatic or asymptomatic to reduce the risk of congenital toxoplasmosis.[7,12]

WHO and the Centers for Disease Control and Prevention recommend administration of pyrimethamine, sulfadiazine, and folinic acid as the standard therapy in patients with congenital toxoplasmosis. These drugs have been shown to be useful in a randomized prospective study conducted by the National Collaborative Chicago Based Congenital Toxoplasmosis Study (NCCBTS). In this study it was found that these three drugs significantly reduced the symptoms and clinical findings associated with congenital toxoplasmosis such as central nervous system manifestations, ocular, and sensorineural hearing loss. In patients who are hypersensitive to sulfadiazine, clindamycin can be used as an alternative.[7]

Figure 2 above explained the approach for management of pregnant women with toxoplasmosis infection. In patients with suspected acute maternal toxoplasmosis, spiramycin should be given immediately at a dose of 2-3 grams per day. This drug does not cross the placental barrier, but can reduce the risk of vertical transmission by nearly 60%. If the PCR of amniotic fluid shows a positive result, a bacteriostatic therapy that can cross the placental barrier should be given because it is likely that a fetal infection has occurred. The goal of this treatment is to reduce the risk of fetal malformations that may occur due to acute toxoplasmosis. Thus, pyrimethamine can be given at a dose of 50 milligrams per day and sulfadiazine 3 grams per day. However, both of these drugs have high teratogenic effects because they reduce serum folate synthesis in the fetus. It is known that low serum folate concentrations can reduce the synthesis of the enzyme tetrahydrofolate reductase. This enzyme works within cells to convert homocysteine, which is a cytotoxic and teratogenic agent, into methionine, which is an essential amino acid. The high concentration of homocysteine in the tissue is one of the causes of structural abnormalities in the fetus. Therefore, sulfadiazine and pyrimethamine should not be given continuously and must be substituted with spiramycin every 3 weeks. Folinic acid should also be given 2 or 3 times a week at a dose of 10 to 20 mg per day, while the patient is taking sulfadiazine and pyrimethamine. The administration of these three drugs reduces the risk of the fetus from severe congenital abnormalities by 70%. However, the most serious side effect of this treatment is bone marrow suppression. This suppression will result in neutropenia, anemia, and thrombocytopenia. This side effect can be avoided by giving folic acid every day. A weekly cell count and platelet count should be performed to monitor the bone marrow suppression effect.[7,13] In our case report we continued giving the spiramycin therapy, due to the knowledge that in the PCR result had a 99% NPV in which a 1% probability of fetal infection still existed.

Postnatal monitoring

After entering the postnatal period, the gold standard for establishing the diagnosis of congenital toxoplasmosis is the persistence of toxoplasma IgG antibodies for 12 months. Conversely, the standard to rule out a diagnosis is a decrease to the disappearance of IgG antibody titers in less than 12 months along with the absence of treatment.[10,14]

The most common laboratory examination method used to diagnose congenital toxoplasmosis in newborns is the serological detection of multiple toxoplasma antibody isotopes in serum. Although there are many specific methods for detecting Toxoplasma antibodies, IgG, IgM, and IgA antibodies should always be checked. PCR examination of cerebrospinal fluid, peripheral blood, and urine can be performed for the initial diagnosis of congenital toxoplasmosis.[10]

Antibody IgG testing, the dye test is the reference method which is the gold standard. However, dye tests can only be done in fully equipped laboratories due to their dependence on using live parasites. Other methods used are enzyme-linked immunosorbent assays and ELISA-like assays, agglutination, and indirect immunofluorescence.[10]

During the postnatal period, detection of toxoplasma IgG can be confused with the presence of maternal IgG that is transferred passively across the placenta to the neonate. Detection of IgM and IgA in neonates can be contaminated with

maternal toxoplasma IgM during the first 5 days of life and maternal toxoplasma IgA persists for the first 10 days of life. To meet this challenge, methods to compare maternal and child IgG, IgM, and IgA have been developed such as Western blotting. Western blotting can make the diagnosis 3 months earlier than conventional serologic methods. The sensitivity of Western blotting with combination of conventional serology is superior compared to Western blotting or conventional serology alone. However, interpretation of Western blots can be difficult and could not be done after a certain age because the test results can be false-positive.[10,14,15]

In our case, serological examinations of IgG and IgM were carried out at the age of 4 days and found positive anti-toxoplasmosis IgG with a concentration of 482 and negative IgM. However, based on the literature this can be caused by the presence of IgG from the mother that is transferred passively through the placenta to the neonate until the fifth day of birth.[16] The pediatric consultant advised that the baby to be rechecked at the age of 3 and 12 months. His results for both IgG and IgM antibodies at 3 and 12 months turned out negative. During observation the baby developed well with no complaints related to toxoplasmosis infection.

CONCLUSION

The diagnosis of toxoplasmosis has many challenges, including the absence of preliminary serological data to determine seroconversion and the difficulty of determining when fetal transmission occurs. It is essential to determine when the infection occurred so that proper management can be carried out.

Diagnosis and screening for toxoplasmosis require a proper understanding of the serological examination and its specificity and sensitivity. Ultrasound monitoring for detection of congenital toxoplasmosis can also aid in the diagnosis.

Until now, there is no strategy that is most effective in detection and management. These differences in guidelines are caused by uncertainty about the benefits of treatment and concerns about the side effects of treatment, as well as the cost and infrastructure required to implement prenatal screening. Therefore our study suggests that a national database might be needed to record the prenatal IgG anti-toxoplasmosis status which then can be used to determine whether seroconversion has occurred during pregnancy.

CONFLICT OF INTEREST

The author states that there is no conflict of interest regarding the publication of this case report.

ETHICS IN PUBLICATIONS

The patient has signed informed consent regarding the publication of medical data in medical scientific journals.

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