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ORIGINAL ARTICLE

Role of spiramycin in prevention of fetal toxoplasmosis

Muhittin Eftal Avci[1], Ferhat Arslan[2], Şinasi Çiftçi[1], Ali Ekiz[1], Abdullah Tüten[3], Gökhan Yildirim[1], and Rıza Madazli[3]

[1]Department of Perinatology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey, [2]Department of Infectious Diseases and Clinical Microbiology, İstanbul Medipol University Hospital, Istanbul, Turkey, and [3]Department of Perinatology, Cerrahpasa Medicine Faculty, Istanbul University, Istanbul, Turkey

Abstract

Objective: The aim of this study is to evaluate the efficacy of spiramycin in prevention of mother-to-child transmission of Toxoplasma gondii infection.
Methods: Patients within first trimester of their pregnancy with Toxoplasma IgM positivity (>0.65 index, ELISA, VIDAS) and IgG positivity (>8 IU/ml), who had low IgG avidity (<0.50 index, ELISA, Architet) were considered as having acute toxoplasmosis. These patients who had amniocentesis at the 19th–21st week of pregnancy were examined for the detection of Toxoplasma DNA. Detailed ultrasonographic examinations performed between the 20th and 24th gestational weeks and the mothers and babies were followed for at least one year.
Results: Out of 61 patients, 55 (90.2%) had received Spy prophylaxis while 6 (9.8%) cases refused Spy prophylaxis. Toxoplasma PCR test was found to be positive in amniotic fluid of 4 (6.6%) patients obtained by amniocentesis at the 19th–21st week of pregnancy. All four of these patients had refused Spy prophylaxis had positive Toxoplasma PCR in amniotic fluid ($p < 0.01$).
Conclusion: Our results seem to encourage the use of spiramycin in women with toxoplasmosis during pregnancy.

Keywords

Amniocentesis, PCR, prophylaxis, spiramycin, Toxoplasma gondii

History

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Introduction

Toxoplasma gondii, which is a widely distributed protozoon, is an infectious agent particularly affecting subjects early childhood and adolescence in the developing countries. If this infection is acquired primarily during pregnancy, it can be transmitted to the fetus and may cause congenital toxoplasmosis (CT) with severe neurologic findings [1]. Previous studies conducted in pregnant women have shown that primary infection in pregnancy may cause congenital infection in an increasing rate: from <10% in the first trimester to 70% in the last trimester [2]. Moreover, if the infection is acquired close to the period of embryogenesis, the resulting clinical impact would be more severe [3]. Although screening of pregnant women in order to prevent this infection and prenatal treatment have been practiced for years, the efficacy of therapy is still a controversial issue [4,5]. Different clinical approaches for those patients are implemented both in European countries and in our country. The primary goal of this study is to evaluate the efficacy of spiramycin (Spy) prophylaxis given in the first 18 weeks of pregnancy for the prevention of CT.

Address for correspondence: Muhittin Eftal Avci, Department of Perinatology, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Halkalı, Küçükçekmece, İstanbul. Tel: +902124955920. Mob: +90505246742. Fax: +902125714790. E-mail: eftal77@ yahoo.com

Materials and methods

This study was designed as a multicenter retrospective trial in the pregnant women with the diagnosis of acute toxoplasmosis (AT). Patients within first trimester of their pregnancy with Toxoplasma IgM positivity (>0.65 index, ELISA, VIDAS) and IgG positivity (>8 IU/ml), who had low IgG avidity (<0.50 index, ELISA, Architet) were considered as having AT. Extended ultrasonographic examinations performed on all fetuses of pregnant women with AT between the 20th and 24th gestational weeks. All the fetuses were followed by ultrasonographic examinations biweekly. The patients with AT who had amniocentesis at the 19th–21st week of pregnancy were examined for the detection of Toxoplasma DNA using polymerase chain reaction (PCR). Template DNA from clinical specimens was prepared using the High Pure PCR Template Preparation kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. PCR was performed using two pairs of primers that anneal to gene B1 of the Toxoplasma gondii, leading to amplification of 690 and 178 bp fragments [6].

At birth, neurological examination, ophthalmoscopy and transfontanellar cranial ultrasonography were performed on the newborns. Based on the patients' files records, mothers and babies were followed for at least 1 year.

The relationship between Toxoplasma positivity at the 19th–21st week of pregnancy and spiramycin (Spy) use was evaluated with chi-squared test.

Results

The medical records of a total of 129 pregnant women with the diagnosis of suspected AT were reviewed retrospectively. Among them, 61 patients having a mean age of 27.2 ± 6.1 years and mean gravida and parity of 2.8 ± 1.2 and 1.6 ± 1.1, respectively, fulfilled the inclusion criteria (Table 1). Remained 68 patients were excluded from study due to high avidity levels despite toxoplasma IgM and IgG positivity. Out of 61 patients, 55 (90.2%) had received Spy prophylaxis while 6 (9.8%) cases refused Spy prophylaxis. Toxoplasma PCR test was found to be positive in amniotic fluid of 4 (6.6%) patients obtained by amniocentesis at the 19th–21st week of pregnancy. All four of these patients had refused Spy prophylaxis had positive Toxoplasma PCR in amniotic fluid ($p < 0.01$). Two fetuses (Patient 1 and Patient 2 at Table 2) had ultrasonographic abnormalities including intracranial calcifications, ventriculomegaly and hepatomegaly in one fetus, and intracranial calcifications, ventriculomegaly, cataracts and hepatomegaly in the other fetus (Figure 1). Termination of pregnancy was performed in the four patients with Toxoplasma PCR positivity upon demand of the patients, who denied permission for autopsy. Other two of the six patients who refused Spy were negative. None of the 55 patients who received Spy prophylaxis had Toxoplasma PCR test positivity. There are no significant differences between the laboratory data of PCR positive patients and those of PCR negative patients (Table 2). The rest of the pregnancies ended up with the delivery of healthy newborns. The 1-year follow-up did not show any congenital abnormalities.

Table 1. Demographic and disease-related characteristics of the patients.

	AT patients ($n = 61$)
Maternal age (years, mean ± SD)	27.2 ± 6.1
Gravida (mean ± SD)	2.8 ± 1.2
Gestational age at diagnosis(week, mean ± SD)	9.8 ± 2.3
Toxoplasma serology	
IgM (mean ± SD)	2.46 ± 1.78
IgG (mean ± SD)	258.03 ± 217.65
IgG avidity (mean ± SD)	0.23 ± 0.11
PCR (+)	4 (6.6%)
Spiramycin prophylaxis	55 (90.2%)
Delivery	
Vaginal	49 (80.3%)
C/S	8 (13.1%)
Termination	4 (6.6%)
Gestational age at delivery (week, mean ± SD)	37.9 ± 2.1
Birth weight (g, mean ± SD)	3590.3 ± 588.6

AT, acute toxoplasmosis; SD, standard deviation; g, gram.

Discussion

Toxoplasma infection generally is asymptomatic but severe complications can occur, most frequently in immunosuppressive patients or congenital infection cases. If maternal infection is verified and there is risk of fetal infection or if infection markers are found on ultrasonography, invasive prenatal diagnosis for fetal toxoplasma infection is required [7]. We have found ultrasonographic findings related to Toxoplasma infections in two of four PCR positive fetuses. In the study of Pratlong et al. [8] ultrasonographic findings indicative of infection were identified in only 4 of 20 infected fetuses (one with hydrocephalus and three with hepatomegaly). In another study, Hohlfeld et al. [9] showed that 32 of 89 infected fetuses had abnormal ultrasonographic markers at 20–32 weeks' gestation. The sonographic findings more prevalent in the fetuses with early infections were similar to those reported in our study.

PCR procedure investigates the presence of the protozoal DNA in the amniotic fluid. On the other hand, the accuracy is highly dependent on the quality of the laboratory performing the PCR and the sensitivity is 40–92% with a negative predictive value of 96–98% [10,11]. This means that a negative test does not always shows the absence of infection. Therefore, we continued the Spy treatment in all the PCR negative cases.

Prenatal invasive diagnosis is generally performed through an amniocentesis, carried out after >18–19 weeks and at least 5–6 weeks after the estimated date of maternal infection [7]. We performed all amniocentesis between 19th and 21st weeks of gestation. When the diagnosis of AT is confirmed, immediate initiation of Spy treatment is recommended [12]. Spy is a macrolide derivative which is used for the treatment of Toxoplasma infection during pregnancy because of its ability to reach high concentrations in the placenta, therefore, to prevent the transmission of the infection to the fetus [13,14]. In some countries, Spy treatment is used until the 16th week of gestation and then the therapy is switched to a combination of pyrimethamine (Pyr), sulfadiazine and folinic acid for 4 weeks, while in other countries Spy treatment is continued until fetal infection is confirmed by means of amniocentesis [15]. If fetal infection is defined by the presence of molecular and/or ultrasonographic findings,

Table 2. Clinical characteristics and laboratory values of PCR (+) patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Maternal age (year)	29	36	34	25
Toxoplasma IgM	6.41	1.52	1.02	3.44
Toxoplasma IgG	242	50	700	75
Toxoplasma IgG avidity	0.16	0.29	0.35	0.27
Gestational age at diagnosis (week)	12	11	12	12
Gestational age at termination (week)	23	22	23	23
USG finding	Intracranial calcification Ventriculomegaly Hepatomegaly	Intracranial calcification Ventriculomegaly Cataracts Hepatomegaly	None	None

PCR, polymerase chain reaction.

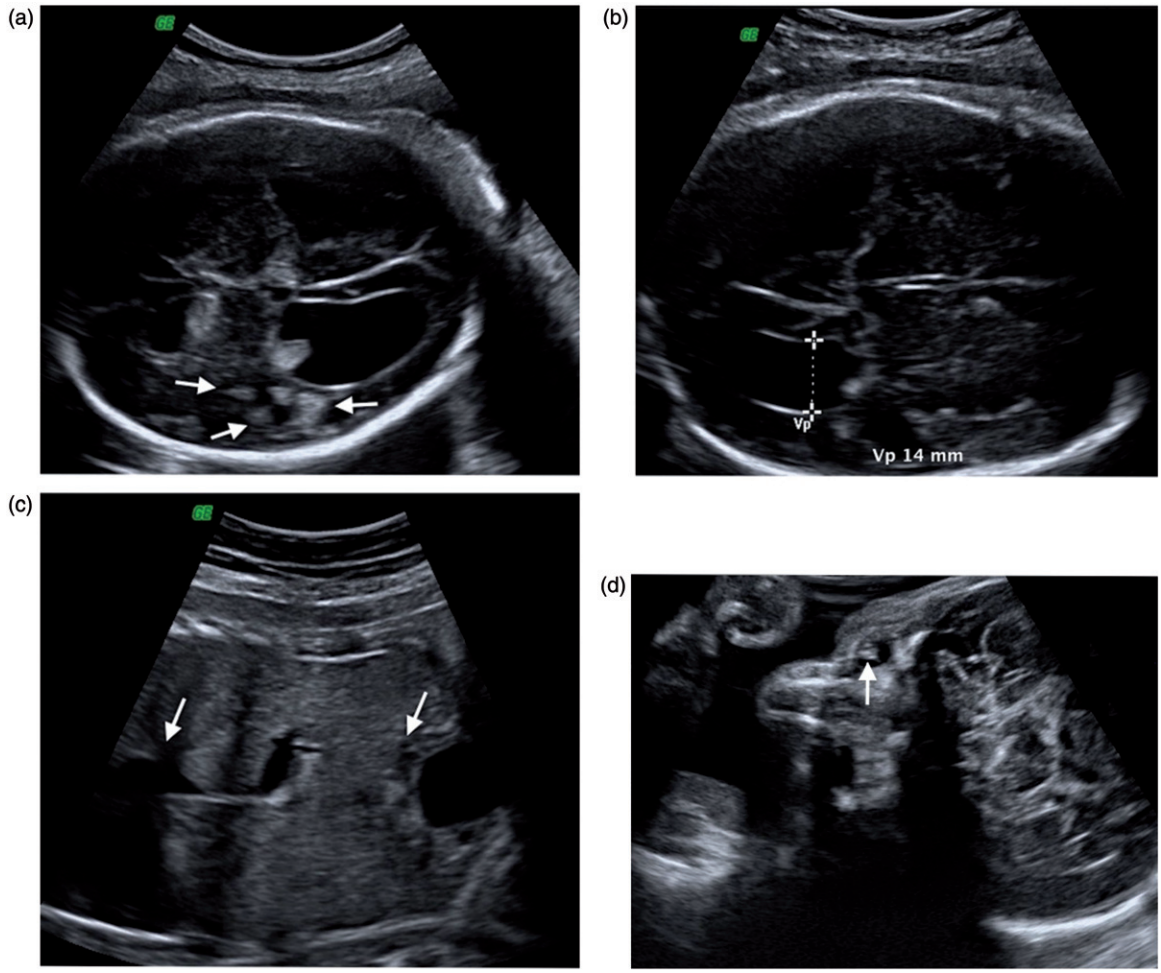

Figure 1. Ultrasonographic images of fetal toxoplasma infection. (a) White arrows indicate periventricular calcification, (b) ventriculomegaly; lateral ventricle width: 14.09 mm, (c) hepatomegaly; white arrows indicate liver borders from diaphragma to urinary bladder and (d) white arrow indicates the fetal cataract.

Spy or Pyr/sulfonamide (Sul) combination therapy is recommended to be continued until the delivery [16].

Prenatal Spy treatment is still a controversial issue today [4,5]. Conflicting results have been obtained from the multicenter studies conducted in Europe. In one of these studies, Spy has been reported to decrease the severe neurological sequela. In another study, 11 patients out of 22 treated with Spy were undergone amniocentesis, and Toxoplasma PCR were negative in all of them [17]. However, in a prospective study evaluating three different treatment groups (Spy monotherapy, Pyr/Sul combination therapy and untreated group) among 1208 cases, prenatal treatment did not show to have any efficacy in prevention of fetal transmission [18,19]. Contrary to our study, in a retrospective study including 120 pregnant women suspected to have primary toxoplasmosis, Spy monotherapy, Spy/cotrimoxazole (Spy/C) and Pyr/Sul combination therapies were compared with each other, and congenital infection has been reported to occur more in the Spy arm ($p = 0.014$) [20]. One of the major limitations of our study was that it includes only pregnant women with suspected Toxoplasmosis in the first trimester during which the risk for fetal infection is low. The main reason for including pregnant women in the first trimester is that most of the obstetricians in our country screen the pregnant women for congenital infection routinely in that period. The decision of termination of pregnancy or prenatal treatment is made mostly in the first trimester. Another limitation of our study is that we failed to confirm the presence of fetal infection in the two fetuses with Toxoplasma PCR positivity. Despite the normal ultrasonographic findings, the request of the two patients for termination of pregnancy highlights the significance of this issue.

In conclusion, our retrospective study showed that Spy could be efficient in prevention of fetal infection, supporting the use of Spy in pregnant women with AT in the first trimester of pregnancy.

Declaration of interest

The authors have no conflicts of interest to declare.

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