Investigation of the Incidence and Perinatal Outcomes of Acute Toxoplasma Infection in Pregnancy: Results from the Tertiary Center of the Eastern Black Sea Region

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Abstract: *Objective*: Toxoplasma gondii is a common protozoan that can infect humans in various ways. Parasitic infections, which usually affect humans in childhood and adolescence, can be transmitted from mother to fetus if it occurs for the first time during pregnancy and it may result in a congenital toxoplasma infection.

The aim of the study is to determine the incidence of acute toxoplasma infection during pregnancy and to evaluate the perinatal outcomes.

Materials and Methods: The study has been designed as a retrospective analysis of the data of all pregnant women who had attended the pregnancy outpatient clinic of the Department of Obstetrics and Gynecology at Karadeniz Technical University between 2014 and 2018. Patients within the first trimester of their pregnancy with Toxoplasma IgM positivity (≥ 1 index, ELISA, Elecsys®) and IgG positivity (≥ 3 IU / ml, ELISA, Elecsys®), who had low IgG avidity (<70% (ELISA, Elecsys®) were considered as having acute toxoplasmosis. Detailed ultrasonographic examinations were performed between the 20th and 23rd gestational weeks and the mothers and babies were followed up for over the ensuing six months.

Results: The total number of patients for whom the results of toxoplasma Ig tests were ordered was 11,045 and, of these patients, 157 were found to be both Ig M and Ig G positive. 29 of these 157 patients was with low Ig G avidity. So the incidence of acute toxoplasmosis was 0.26% in this clinic. The mean age of the 29 patients with low Ig G avidity was 28.86 +/- 4.69. All 29 patients agreed to receive antibiotic prophylaxis with Spiramycin and, consequently, they received Spiramycin prophylaxis during pregnancy. Of the patients diagnosed with acute toxoplasmosis; Toxo Ig M mean value was 4.58 +/- 4.60; Toxo Ig G mean value was 332 +/- 265.42 and Toxo Ig G avidity wasfound to be 50.37 +/- 14.16%. No pathological features were found in the postnatal follow-up of 26 babies who were delivered at the clinic.

Conclusion: Toxoplasma screening should be performed routinely for fetal morbidity and mortality during the first trimester of pregnancy in high-risk areas. Pregnant women should be informed about pre-natal counseling programs and first trimester applications with educational materials containing messages about the prevention of infection.

Keywords: Toxoplasmosis, pregnancy.

INTRODUCTION

Toxoplasma gondii is a common protozoan that can infect humans in various ways. The parasitic infection, which usually affects humans in childhood and adolescence [1], can be transmitted from mother to fetus if it occurs for the first time during pregnancy and may result in a congenital toxoplasma infection. While the frequency of congenital toxoplasma infections increase with progressive gestational weeks, the severity of the clinical picture is higher when acquired during the early weeks of gestation [2,3]. Although it varies according to the development levels of a country; the incidence of acute toxoplasma infection during pregnancy has been reported to be between 0.1-0.8 per 100 [4].

Congenital toxoplasma infection is a clinical condition that occurs following an acute infection during pregnancy and is usually seen with neurological abnormalities and varies from one country to another, but it is reported as 1 in 1000 in developing countries, and 1 in 10000 in developed countries such as the United States [5,6]. Congenital toxoplasmosis is recognized by its classic triad; chorioretinitis, hydrocephalus and intracranial calcifications. This triad occurs in less than 10% of cases [7]. In cases of acute toxoplasmosis, routine screening for toxoplasma infection together with the recommendation of prophylaxis, where necessary, can help to prevent the patient from developing congenital toxoplasmosis which can have severe neurological consequences [8,9].

The aim of this study was to publish data on the incidence of toxoplasma infection at the tertiary perinatology clinic of the Black Sea, to draw attention to the importance of prophylaxis of spiramycin for these pregnant women and to investigate neonatal outcomes.

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MATERIALS AND METHODS

The study was designed as a retrospective analysis of the data of all pregnant women who had applied to the pregnancy outpatient clinic of the Department of Obstetrics and Gynecology at Karadeniz Technical University between 2014 and 2018.

The toxoplasma serologies of pregnant women who attended for toxoplasma screening in the first trimester were examined and the pregnant women diagnosed with acute toxoplasma infection were identified. In the first trimester of pregnancy; Toxoplasma Ig M positivite (≥ 1 index, ELISA, Elecsys®), Ig G positivite (≥ 3 IU / ml, ELISA, Elecsys®), and, if two positives were found, the desired Ig G avidity test which indicated low avidity (<70% (ELISA, Elecsys®), patients were diagnosed as having acute toxoplasmosis and followed up by theperinatology clinic. Spiramycin was begun as prophylaxis in patients who underwent detailed fetal evaluations between the 20th and 23rd weeks of gestation and the patients were instructed to use them throughout their pregnancy. Toxoplasma DNA investigation by PCR (polymerase chain reaction) technique with amniocentesis was recommended for all patients for a definitive diagnosis of infection.Postnatal neurological examinations of the babies whose births were performed in the clinic were investigated and followed-up by performing ophthalmoscopy and transfontanel cranial ultrasonography. The babies were followed up for a period of at least six months.

The local Ethics Committee approved the study. (Karadeniz Technical University Ethics Committee, 2019/288). The study was created based on the principles set out in the Declaration of Helsinki.

Statistical Analysis

The SPSS 20 program designed for Windows was used for statistical analysis.

All continuous variables were defined as mean and standard deviations. Categorical variables were shown as a percentage of the total group.

RESULTS

The records of a total number of 11,045 women were initially obtained from the hospital's data-processing records for patients who had attended the obstetrics clinic during the first trimester of their pregnancies between 2014 and 2018 and for whom a test for toxoplasma Ig had been undertaken.

157 of these patients were both Ig M and Ig G positive. The number of patients with low Ig G avidity was 29 of these 157 patients. Therefore, the incidence of acute toxoplasmosis was determined to be 0.26%. Despite the Ig M and Ig G positivity of the remaining 128 patients, the Ig G avidity test was found to be high and was excluded from the study because it did not meet the definition of acute toxoplasmosis.

The mean age of the 29 patients with low Ig G avidity was 28.86 +/- 4.69. The mean gravida and parity values were 2.17 +/- 1.17 and 1.00 +/- 1.1, respectively.

The demographic characteristics of the 29 patients diagnosed with acute toxoplasmosis are shown in Table **1**.

Table 1: Demographic Characteristics of the Patients (Patients with Acute Toxoplasmosis, n=29)

Maternal age, years	28.86 ± 4.69 (21-37)
Gravida, median	2 (1-5)
Parity	1.0 ± 1.10 (0-4)
Gestational age at diagnosis, weeks	9.79 ± 2.58 (5-13)
History of animal contact during pregnancy	11/29 (37.9 %)
History of eating raw meat during pregnancy	12/29 (41.4 %)

All 29 patients agreed to receive antibiotic prophylaxis with Spiramycin and received Spiramycin prophylaxis during their pregnancy. All 29 patients were advised to undergo an investigation of the Toxoplasma antigen from the fluid obtained by amniocentesis, but 22 patients declined to accept. Only seven patients underwent amniocentesis and Toxoplasma PCR was performed. None were positive. The patient characteristics associated with acute toxoplasmosis are shown in Table **2**.

Table 2: Acute Toxoplasmosis - Related Characteristics of the Patients

Toxoplasma serology	Patients with acute toxoplasmosis (n=29)
Toxo Ig M (index)	4.58 ± 4.60 (index) (1.17-20.96)
Toxo Ig G (IU/ml)	332 ± 265.42 (IU/ml) (18.85-650)
Toxo Ig G avidity (%)	50.37 ± 14.16 (%) (1.30-69.52)
PCR (+) by amniocentesis	0/29 (0 %)
Spiramycin prophylaxis	29/29 (100 %)

Of the patients diagnosed with acute toxoplasmosis; Toxo Ig M mean value was 4.58 +/- 4.60; Toxo Ig G mean value was 332 +/- 265.42 and Toxo Ig G avidity was found to be 50.37 +/- 14.16%.

While 14 of the 29 patients delivered by vaginal delivery, no termination of pregnancy was recommended for any fetus as detailed ultrasonography showed no signs of toxoplasma infection. The birth-related characteristics are shown in Table **3**.

Table 3: Birth-Related Characteristics of the Patients with Acute Toxoplasmosis (n=29)

Vaginal delivery	14/29 (48.3 %)
Cesarean section delivery	15/29 (51.7 %)
Termination of fetus	0/29 (0%)
Gestational age at delivery (week, mean +/- sd)(min-max)	37.5 ± 1.24 (34-40)
Birth weight (g, mean +/- sd)(min-max)	3108 ± 378.9 (2500 - 3820)
Gender of baby (female/male)(%/%)	15/14 (51.7 % / 48.3 %)

No pathological features were found in the postnatal follow-up of 26 babies who were delivered at the clinic and in the neurological examinations performed by pediatric neurology in the postnatal third to sixth month periods. There was no evidence of chorioretinitis in the ophthalmologic examination of the infants, and transfontanel cranial ultrasonographic examinations were normal.

DISCUSSION

Toxoplasmosis, which is mostly asymptomatic in healthy individuals, can result in serious clinical conditions as a result of primary infection during pregnancy [2,10]. Primary infection with T gondii is rare during pregnancy and is difficult to diagnose. The major consequence of a primary infection is the vertical transmission to the fetus resulting in congenital toxoplasmosis [11].

Although the prevalence of congenital toxoplasmosis decreases every year [12,13], toxoplasmosis still poses a threat to human health. Between 1986 and 1999, data from 127 studies that investigated toxoplasma seroprevalence in women in the reproductive age group in 53 countries was collectively evaluated jointly and the seroprevalence in the reproductive age group was found to be 42%. It is estimated that approximately 2.5 billion people in the world are infected with T. Gondii [14]. The prevalence of toxoplasmosis in our country varies between 40–80 % [15]. In a study of 1,122 pregnant women between 1993 and 1994, Göl *et al*. found that the rate of acute infection was 0.35 % [16]. In 2008, Durdu *et al*. conducted a study of 102 toxoplasma IgM positive pregnant women with no acute toxoplasma infection (0 %) [17]. In the current study, when the four-year data was examined, a 0.26% incidence of acute toxoplasma infection was found in pregnant women with toxoplasma positivity. Due to the fact that this study scans a wider time interval and a large number of cases, it can be seen to be superior to other studies. According to this data, it can be stated that acute toxoplasma infections have decreased over the years.

The main transmission routes of toxoplasmosis are through the consumption of raw meat, the consumption of poorly washed vegetables and contact with animals (cats). In the current study, 11 cases (37.9%) had had animal contact and 12 cases (41.4%) had eaten raw meat. Seroprevalence varied depending on age, geographical location, hygiene conditions, life habits, nutritional status and frequency of contact with cats.

Toxoplasmosis during pregnancy causes intrauterine malformations, miscarriages and preterm births, and may cause congenital toxoplasmosis in newborns [18,19]. Congenital Toxoplasmosis may occur especially in the babies of pregnant women infected with toxoplasma in the first trimester. The classic triad of congenital toxoplasmosis in the fetus is hydrocephalus, intracranial calcification and ocular lesions [20]. However, it is possible to reduce the negative fetal effects if diagnosed and treated in a timely manner. Exposure to toxoplasmosis should be evaluated and avoidance recommendations should be given to women considering pregnancy [21]. Education should be provided to reduce the transmission of Toxoplasma gondii, infection and, hence, congenital toxoplasmosis.

However, despite the success of some observational studies, several studies (including a Cochrane review) have shown that weaknesses in the study design have prevented any conclusion that such strategies reduce congenital toxoplasmosis [22]. There is little evidence that prenatal education is effective in reducing congenital toxoplasmosis. More randomized controlled trials are needed.

In a bulletin published in 2015, ACOG does not recommend routine serological screening for pregnant

women for toxoplasmosis. It has been reported that routine screening is unnecessary because approximately 38% of pregnant women have toxoplasma Ig M positivity and relatively low seroprevalence. Due to the low incidence of acute infection, ACOG does not recommend screening for all pregnant women due to the lack of standardized serological tests outside the reference laboratories, the high cost, and the unnecessary diagnosis of a large number of women [23,24]. In the United States, they argue that prenatal screening for toxoplasmosis should be limited to women who are immunosuppressed or human immunodeficiency virus (HIV) positive [22].

The risk and severity of infection in the fetus depends on the trimester in which the infection develops. While the rate of passing toxoplasmosis to the fetus in the first trimester is 10-25%, it is 30-54% in the second trimester and 60-65% in the third trimester [25]. While the risk of fetal involvement is 75% in the first trimester, it is close to 0% in the last trimester [26].

If maternal infection is treated, the risk of the fetus developing a congenital infection is reduced by 60%. Toxoplasmosis seroprevalence in the world varies between 12% and 90% depending on the risk factors for transmission [27]. In the current study, prophylactic spiramycin was administered to all patients with a low avidity test during their pregnancy.

In the literature, despite numerous studies conducted over the last 30 years, it is still not known whether prenatal treatment in Toxoplasma gondii reduces the congenital transmission of toxoplasmosis in pregnant women. In the studies, it has been stated that it is necessary to evaluate the effects of prophylactic treatment and the effect of screening programs because screening is expensive.

Since toxoplasma prevalence, raw meat eating habits and animal husbandry are higher than in the west, toxoplasma is examined within the scope of routine screening in the Eastern Black Sea region.

Spiramycin is used in cases with Toxoplasma positivity and a high risk of transmission.

In general, higher seropositivity rates are observed in cities in the Southeast in comparison with cities in the Black Sea region [28].

The fact that many in the region rely on livestock for their livelihood, together with the fact that food made from raw meat is a part of the region's culture, increases the frequency of toxoplasma.

Between 2009 and 2012, seroprevalence of toxoplasma was evaluated in the Central-Black Sea region and toxoplasma Ig M was found to be positive (1.1 %) in 36 patients out of 3162 pregnant women [29]. When the literature was examined, no data relating to toxoplasma during pregnancy was found in the Eastern Black Sea region.

The weakness of the current study is the low number of cases with the disease, the absence of an affected fetus, the absence of any anomaly in the postpartum period, and the retrospective nature of the study. The fact that it is the first study to evaluate the incidence of toxoplasma and perinatal outcomes in pregnancy in the Eastern Black Sea region makes it worthwhile for prospective studies that should include a larger number of cases. In the Eastern Black Sea region, the incidence of acute toxoplasma in pregnancy is higher than in developing countries.

Toxoplasma screening should be performed routinely for fetal morbidity and mortality during the first trimester of pregnancy in high-risk areas (such as the Eastern Black Sea). Pregnant women should be informed about pre-natal counseling programs and first trimester attendances with educational materials containing messages about the prevention of infection.

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