

Preventing congenital toxoplasmosis — implementation of clinical practice guidelines

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ABSTRACT

Objectives: The aim of the study was to evaluate obstetric care of pregnant women with regard to prevention of congenital toxoplasmosis. Additionally, we attempted to determine the frequency of markers for past infection with *Toxoplasma gondii* in order to characterize the current significance of preventive measures in the Polish population.

Material and methods: The analysis of the medical records — pregnancy charts of women who presented for delivery — was performed. Patient age, place of residence, and toxoplasmosis test (or lack of it) were evaluated. Also, further diagnostic management, depending on the serologic result, was investigated.

Results: Out of 670 pregnant women, 628 (93.73%) underwent at least one toxoplasmosis diagnostic test. Out of those, 502 (73%) had a negative result (IgG –, IgM –), and 2 (0.32%) had a positive result (IgG +, IgM +), while history of infection with *Toxoplasma gondii* was confirmed (IgG +, IgM –) in 124 (19.75%) cases. Repeat testing was required in 183 (29.14%) out of the 628 women.

Conclusions: A high rate of women in whom IgG antibodies were not detected in the first test and a low rate of women who required repeat testing later in pregnancy are noteworthy. Regardless of the healthcare policy, parents should receive reliable information about the nature of the disease and possibilities of prevention, while medical professionals ought to have easy access to research data about the epidemiologic status and recommendations.

Key words: obstetric care, prophylaxis, seroprevalence

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INTRODUCTION

Toxoplasmosis remains to be one of the most common parasitic zoonoses and constitutes a serious threat to neonates born to mothers with an active infection during pregnancy. The global literature reports significant diversity in terms of women who exhibit anti-*Toxoplasma* antibodies, which confirms past infection. According to meta-analyses which investigated studies in women of the reproductive age between 1990 and 2000, a high (over 50%) rate of seropositive results was found in Central Europe, Latin America, and eastern Africa. Significantly lower rates have been reported for inhabitants of eastern Asia, Scandinavian countries, and the US [1, 2]. The results are often conflicting, even within the investigated countries. Furthermore, various

authors have emphasized the role of patient age, place of residence, and climate, as well as contact with cats, agriculture jobs, dietary habits and hygiene [3].

Human hosts become infected with *Toxoplasma gondii* at various stages of its development: oocysts excreted by a cat through food, water, dirty hands, cysts from contaminated meat, trophozoites which overcome the placental barrier to the fetus or, albeit rarely, through blood and blood product transfusions or transplant [4]. Acquired toxoplasmosis is typically oligosymptomatic, with lymphadenopathy of the neck glands, flu-like symptoms, fever, muscle pain, headache, and fatigue. On rare occasions, the disease leads to a general infection, affecting the liver, lungs, heart muscle, skeletal muscles, and brain. Often, seroconversion is the only proof of past

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infection due to indistinct symptoms [5]. Primary infection in a pregnant woman presents a particularly challenging issue for obstetricians and neonatologists due to the potential risk of transplacental transmission and fetal infection. The risk for transmission increases with gestational age while symptom intensity increases with duration of pregnancy. In the first trimester, the infection may result in miscarriage or intrauterine fetal death. In the other trimesters, it may lead to non-immune hydrops fetalis, hydrocephaly, microcephaly, intracranial calcification, or retinitis. Damage to the fetus may result in blindness, disturbed psychomotor and mental development, preterm labor, intrauterine growth restriction, and neonatal demise [6]. Long-term studies on the effects of past infection on disturbed brain function and behavior have also been published [7].

As far as prevention of the congenital infection is concerned, early diagnosis of seroconversion in a seronegative pregnant woman is vital as immediate and effective therapy prevents the protozoan from transplacental transmission. Toxoplasma-specific IgG and IgM antibodies are used to determine the serologic status of a pregnant woman [8, 9]. Early diagnosis and immediate treatment of the mother play the key role in toxoplasmosis prevention. Attitudes to prevention of toxoplasmosis vary around the world. In Poland, the first toxoplasmosis test is recommended at 10 weeks of gestation. Repeat testing is recommended for seronegative women between 21 and 26 weeks of gestation. Preventive measures include avoidance of raw, rare and under-cooked meat and its products, thorough hand washing and cleaning of the utensils after contact with meat, washing fruit and vegetables, keeping food away from cockroaches and flies, drinking boiled water and milk, thorough washing of hands after contact with soil or use of protective gloves, and avoidance of objects which might have been in contact with cat feces. Pregnant women who dwell in low-risk countries should avoid trips to high-risk countries [10].

Objectives

The aim of the study was to evaluate obstetric care of pregnant women with regard to prevention of congenital toxoplasmosis. Additionally, we attempted to determine the frequency of markers for past infection with *Toxoplasma gondii* in order to characterize the current significance of preventive measures in the Polish population.

MATERIAL AND METHODS

The study was conducted between December 1, 2016 and April 30, 2017 in four public hospitals (1 tertiary and 3 secondary referral centers) of the Wielkopolskie Region. Local Ethics Committee approved of the study. The analysis of the medical records — pregnancy charts of women admitted for delivery — was performed. Patient

age, place of residence, and toxoplasmosis test (or lack of it) were evaluated. Also, further diagnostic management, depending on the serologic result, was investigated. Out of the 800 pregnancy charts, 670 charts with comprehensive and complete data were included in the study. Statistical analysis was performed with JMP PRO12 software, using Chi square test. The α value of = 0.05 was considered as statistically significant.

Study population

Women aged 18–44 years were admitted for delivery during data collection, with subjects aged 21–30 years (55.07%) as the largest group, followed by 31–40 years (276 women; 41.19%), < 20 years (16 women; 2.39%) and > 40 years (9 women; 1.34%). An overwhelming majority of the parturients (517 women, 77.4%) were city dwellers, and the remaining subjects were inhabitants of rural areas (151 women, 22.6%). The charts were collected between 32 and 41 weeks of gestation. Out of the women who presented for delivery, 150 (22.39) were admitted at 36 weeks of gestation and 520 (77.61%) between 37 and 42 weeks of gestation.

RESULTS

Out of 670 pregnant women, 628 (93.73%) underwent at least one toxoplasmosis diagnostic test, and 42 (6.27%) did not undergo the test. Out of the 628 (100%) women, 502 (73%) had a negative result (IgG –, IgM –), and 2 (0.32%) had a positive result (IgG +, IgM +), while history of infection with *Toxoplasma gondii* was confirmed (IgG +, IgM –) in 124 (19.75%) cases. Pregnancy charts of women who seroconverted during pregnancy were excluded from the analysis. Repeat testing was required in 183 (29.14%) out of the 628 women who underwent the test (Tab. 1).

No statistically significant differences were found in serologic results between different age groups, or between city dwellers and inhabitants of rural areas.

DISCUSSION

The analysis of pregnancy charts revealed that 628 (93.73%) women underwent toxoplasmosis testing at least once during pregnancy, but repeat testing was

Table 1. Repeat serologic testing, depending on the primary result

Primary result	Number (%)	Repeat testing number (%)	No repeat testing number (%)
Negative result (IgG –, IgM –)	502 (100%)	170 (33.86%)	332 (66.14%)
Past infection (IgG +, IgM –)	124 (100%)	11 (8.87%)	113 (91.13%)
Positive result (IgG +, IgM +)	2 (100%)	2 (100%)	0 (0%)

performed in only 183 (29.14%) subjects. The number of seronegative women, i.e. at risk for primary infection during pregnancy, is important in the prevention of congenital toxoplasmosis. In their case, repeat testing is recommended between 21 and 26 weeks of gestation. The authors of a study from 2007, published in Polish Gynecology, evaluated only the fact that the test was or was not performed, without the analysis of repeat testing in seronegative women. They also demonstrated that a single toxoplasmosis test was conducted in over 90% of the parturients, and observed a high rate of seronegative IgG women (80% of the respondents) [10].

In our study, as many as 520 (73%) women had negative results for both, IgG and IgM, but repeat testing was performed in only 170 (33.89%) subjects. Studies conducted between 1997 and 2003 are scarce, but the reports from Łódź and Giżycko confirmed the number of seropositive women to be significantly higher (41.3% and 44.29%, respectively) [11, 12]. A study on toxoplasmosis from the Wielkopolska Region, conducted between 1990 and 2000, also reported a significant decrease in the number of seropositive pregnant women, from 58.9 to 43.7% [13]. The Polish studies are historical in nature but more up-to-date findings have been published for other countries, where screening for toxoplasmosis in pregnancy is more common and has been carried out for years. In Austria, a significant drop was observed between 1995 and 2012, from 43.3 to 31.5%, while the age-standardized seropositive rate in the US also dropped from 14.1 to 6.7% among native inhabitants between 1988 and 2010 [14].

Nevertheless, the decreasing rates of seropositive women are associated with elevated risk for primary infection with *Toxoplasma gondii* during pregnancy. Between 2008 and 2016, the National Institute of Hygiene reported notably increased morbidity and incidence rates of congenital Toxoplasmosis (8; 1.93/100 000 — 20; 5.42/100 000, respectively). The lowest (3; 0.72/100 000), and the highest (21; 5.60/100 000) numbers were observed in 2009 and 2014, respectively [15–19]. Several European countries have launched free of charge screening programs for Toxoplasmosis in pregnant women. Austria, France, and Slovenia recommend the first testing to take place in the first trimester of pregnancy, and repeat testing to be performed in the second and third trimesters, with the exception of France, where the test is repeated every month until the end of pregnancy [20, 21]. Countries where such preventive free of charge programs for pregnant women are not available, have created algorithms which include a combination of serologic, biological and molecular diagnostic methods, allowing for a quick diagnosis and timely treatment of the infected mothers and/or the newborns [22]. Some of the abovementioned studies have demonstrated a lack of correlation between the presence of antibodies to *Toxoplasma*

gondii and age or place of residence, which is consistent with our findings, indicating the need to offer the same care to all women, regardless of their age and place of residence.

Lack of continuity of serologic testing during the next trimesters of pregnancy in a significant number of seronegative women is an alarming finding in our study. We also investigated why repeat testing was performed in 11 (8.87%) women who tested positive for IgG but negative for IgM, which is indicative of a past infection. A detailed analysis revealed that in 8 of the women the repeat test was ordered due to high concentrations of IgG antibodies (10.8–606 IU/mL) in the first test, which was the correct course of action as significant increase of IgG antibodies in the maternal serum may be suggestive of an activation of the infection. However, in the remaining 11 women the IgG values were not high and IgM antibodies were not observed, so we were not able to find a rational reason why repeat testing was ordered. Out of the seronegative women, 4 underwent only IgM testing (negative IgM test result), and out of the women with history of past infection, 1 underwent only IgG testing (positive IgG test result). According to guidelines, the IgM test alone is of little value due to the fact that it does not determine past infections, whereas the IgG test alone allows to refrain from further testing procedures. Importantly, the guidelines should be followed, especially the requirement to perform the first test early in pregnancy and repeat testing in the next trimesters. In Poland, the test is not free of charge, which might be the reason why < 100% of the women take the test in the first place, and why only 33.89% seronegative women repeat the test. However, others reasons, apart from the financial aspect, should also be considered, as in France and Austria — countries with considerable experience with free of charge screening — repeat testing is also often omitted. Attempts have been made to introduce a means of control for the testing process by national health institutions [23].

In our study, we found no cases of seroconversion — patients with a confirmed infection during pregnancy receive further care and treatment, and after delivery are most probably immediately transferred to the pathology of pregnancy ward. The 2 women (aged 24 and 30, respectively, and both were city dwellers) who tested positive underwent further diagnostic testing and received parasitological consultation, which excluded the threat for the current pregnancy and found no basis for antiparasite treatment.

Primary infection with *Toxoplasma gondii* during pregnancy, if left untreated, leads to multi-organ complications, including fetal or neonatal death. Questions about the effectiveness of therapy for placental transmission and the possible damage to the fetus, in other words the rationale behind preventive treatment, have been raised. Multi-center studies from several European countries have found no cor-

relation between the treatment and the transmission. However, children born to mothers who received treatment were significantly less affected. Also, timely intervention proved to be important [24], although another meta-analysis (2007), did not confirm the link between early (up to 3 weeks from the diagnosis of seroconversion) and late (8 or more weeks) intervention in terms of maternal-fetal transmission and clinical symptoms of the fetal infection [25]. Regardless, the literature offers numerous reports on severe complications in fetuses of mothers who received the therapy too late, so further studies on benefits of treating Toxoplasmosis in pregnancy are necessary [26].

It is important to be aware of the differences between Poland and other countries as far as guidelines and testing procedures for Toxoplasmosis prevention are concerned. Data from France and the US, where both, the epidemiologic situation and various preventive strategies against congenital Toxoplasmosis are different, have been compared. The number of seronegative pregnant women is significantly higher in France as compared to the US (37% and 9.1%, respectively), the incidence among seronegative women is also higher (2.1/100 000 and 0.2/100 000, respectively), as well as the incidence of congenital Toxoplasmosis (2.9/100 000 and 0.5/100 000, respectively). Due to the abovementioned epidemiologic situation, France introduced a free of charge screening program over 30 years ago. In the US, lack of a large-scale screening program does not allow to detect new cases of infection with *Toxoplasma gondii* among pregnant women. As a result, treatment is not introduced and a significantly higher rate of severely affected children has been reported as compared to France (77% and 3%, respectively) [27].

Regardless of the abovementioned studies, detailed analysis about the benefits of introducing a screening program have been performed. Taking into account all epidemiologic differences associated with Toxoplasmosis in the US, screening of pregnant women, even despite testing and therapy costs, has proven to be cost-saving [28].

The possibilities of screening continue to change, which is associated with the epidemiologic situation as well as quality and cost of testing. New tests, which require a small amount of blood and allow for a faster and cheaper testing of both, the mother and the child, continue to appear on the market [29, 30].

Also, health education has been given more attention as far as Toxoplasmosis prevention is concerned. However, healthcare professionals seem to be focused predominantly on adequate performance and fail to devote sufficient amount of time to educating their patients. It is necessary to integrate clinical medicine with public and environmental health, which might result in spectacularly improved outcomes [31]. Apart from the abovementioned educational

measures targeting people at direct risk for infection, the French studies have emphasized the need to reach to livestock producers and meat processing factories [32]. In our study, we were not able to evaluate the educational initiatives among pregnant women, but the studies from the Institute of Mother and Child in Łódź and County Hospital in Pabianice on the state of knowledge about Toxoplasmosis among ob-gyns, midwives, and pregnant women have revealed insufficient knowledge about the matter among the future mothers [33]. At present, health education in Poland conducted among pregnant patients by doctors and midwives from 21 weeks of gestations ought to include Toxoplasmosis control and prevention.

In conclusion, the high rate of women with undetected IgG antibodies on first testing and the low rate of women who underwent repeat testing are important findings of our study. Regardless of the healthcare policy, parents should receive reliable information about the nature of the disease and possibilities of prevention, while medical professionals ought to have easy access to research data about the epidemiologic status and recommendations. Furthermore, it is important to continue studies of screening profitability and diagnostic testing, as they will allow for simple and inexpensive diagnostic procedures for both, the mother and the child.

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