



Congenital Toxoplasmosis in Israel: To Screen or Not to Screen

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Toxoplasma gondii is an obligatory intracellular parasite, whose exclusive definitive hosts are animals from the cat family. Following the complete sexual life cycle in the cat's intestine, oocytes are formed and excreted in the stool. In humans the infection may be acquired in several ways: a) ingestion of oocytes through close contact with infected cat or cat's feces, b) ingestion of water or food contaminated with the oocytes, or c) eating raw or undercooked meat from infected animals that contain the tissue cysts. In Israel there are no data on the prevalence of contaminated food. In the United States it was found that 8–25% of commercial beef, pork or lamb is contaminated with *Toxoplasma* tissue cysts.

Parasitemia associated with primary infection during pregnancy may cause placental and fetal infection, but as a rule, relapse of the infection in a seropositive pregnant woman carries no risk to the fetus. Nonetheless, the parasitemia associated with primary maternal *Toxoplasma* infection during pregnancy may cause placental and fetal infection. Fetal infection occurs in about 40% of cases, ranging from 15% in the first trimester to 60% in the third. Most pregnant women are asymptomatic during the acute disease, as are most infected infants at birth (up to 85%). Unfortunately, the majority will develop serious sequelae during childhood, such as mental retardation, seizures, hydrocephalus, sensorineural deafness, chorioretinal disease (leading to blindness in up to 85% if untreated), and even death [1,2]. However, it was shown that when pregnant women were treated with spiramicin during acute toxoplasmosis before fetal infection was demonstrated, the frequency of fetal infection declined from 72% to 39%. Furthermore, once fetal infection was diagnosed, a combination of treatment with pyrimethamine and sulfadiazine of the pregnant women and postnatal therapy of the infected newborn reduced both the severity of the infection and the long-term complications in children [1,2].

In this paper we review the available data regarding the need for screening pregnant women or newborn babies for congenital infection, with particular emphasis on Israel.

In the USA, where the seroprevalence rate among pregnant women is 14–23%, the frequency of congenital toxoplasmosis was estimated to be 1:1,000–1:10,000 live births [3,4]. Other epidemiologic studies show that in most western countries the prevalence of congenital toxoplasmosis is similar to that in the U.S. This prevalence is at least equal or even higher than that of congenital hypothyroidism or phenylketonuria (1/4,000 and 1/20,000 respectively), suggesting that screening for the infection may be beneficial [5,6].

In recent years new epidemiologic data have been collected and published regarding the prevalence of toxoplasmosis in the general population during the reproductive years in Israel [7–10]. In all studies, the Sabin-Feldman dye test was the technique used. In these studies the overall *Toxoplasma* seroprevalence among the Jewish population was 13.6–30% in the 10–19 year age group and about 40% in those over 45 years old (mean increase of 0.6% per year). In one study [8], *Toxoplasma* seroprevalence in the rural Arab population in northern Israel increased from 49% at age 20 to 74% at age 40 (an increase of about 1.25% per year). Among the possible explanations suggested for the high seroprevalence in Arabs were different socioeconomic and hygienic conditions and profound differences in eating habits. The ingestion of raw meat (as in a dish called *kubbeh*) and unpasteurized milk and milk products is very prevalent in this population.

Two studies evaluated the incidence of congenital toxoplasmosis in Israel. Franklin et al. [11] investigated the incidence of primary infection during pregnancy among 213 untreated pregnant Jewish women in northern Israel. The incidence rate was 1.4%, but no cases of congenital toxoplasmosis were diagnosed in the newborns of these women after 3 years of follow-up. We recently studied the incidence of congenital toxoplasmosis in the Arab population in northern Israel in order to both evaluate the need for implementing a prevention program and to carry out a routine screening in this high risk population. The study comprised all full-term Arab babies born at HaEmek Medical Center between September

1996 and April 1997. A sample of 3 ml was taken from the umbilical cord after the baby was born. Specific *Toxoplasma* immunoglobulin M antibodies were determined by enzyme-linked immunosorbent assay on all samples using the ETI-Toxok-M kit (Sorin Biomedica Diagnostics S.p.A, Saluggia, Italy). The claimed sensitivity and specificity of this kit is 100% and 99.8% respectively. A total of 1,623 Arab infants were enrolled in the study. About 40% of the families lived in the city and about 40% were born to mothers younger than 25 years old. All blood samples were negative for *Toxoplasma* IgM. In addition, we evaluated the prevalence of congenital toxoplasmosis in our area during the study period from the official records of the Israel Ministry of Health, and no cases of congenital toxoplasmosis were reported (Dan Miron, personal communication).

Based on the above data, we assume that with an annual rate of about 130,000 births and a 0.6–1.25% seroconversion rate during pregnancy, the expected incidence of congenital toxoplasmosis is < 1/1,000 (less than 130 infected babies per year) [4]. The question that arises is whether a screening program is warranted during pregnancy or after birth in Israel, and how it should be implemented.

There are three ways to approach the mass diagnosis of congenital toxoplasmosis [3,4]:

- Screening all babies at birth.
- Repeated testing during pregnancy of those who are seronegative.
- Targeted screening for infection of pregnant women who are suspected to have primary infection.

Before discussing this issue, one should critically review the available methods for serologic diagnosis and screening of toxoplasmosis. The most reliable, sensitive and specific test for diagnosis of toxoplasmosis is the Sabin-Feldman assay. However, this assay measures only IgG, is time consuming, and requires live parasites. Consequently, it can regularly be performed only in reference laboratories and is thus not appropriate for mass screening. The most widely used tests are commercial ELISA for IgM and IgG. Recently, The Centers for Disease Control in Atlanta conducted extensive evaluation of the six most commonly used commercial IgM kits in the U.S. The sensitivity and specificity rates of these kits ranged from 93 to 100% and 77.5 to 99% respectively [12]. Therefore, by itself, the best use of IgM is its absence to rule out recent infection. The conclusion is that a number of acute cases (infants or mothers) might either be missed or falsely diagnosed. When IgM is present, it is desirable to more precisely refine the assessment of how recently the seroconversion occurred. This is obtained by looking out for a rising titer in convalescent serum specimens or implementing more sophisticated, expensive and laborious immunologic tests such as *Toxoplasma*-specific IgA and specific IgG avidity determination, which are available at highly experienced reference laboratories [4,13]. They are appropriate as confirmatory assays.

Ig = immunoglobulin

ELISA = enzyme-linked immunosorbent assay

Universal serologic screening for *Toxoplasma* IgM in all infants at birth has been shown to be a feasible option. These children could be offered early treatment. Several recent studies have shown that it can be performed by using the filter paper blood spot already obtained from every newborn at routine screening for phenylketonuria and hypothyroidism [5,6,14]. According to the Danish program [5], this would identify at least 75% of all asymptomatic infected newborns who would otherwise be missed. In the U.S. study, 52 of 635,000 infants screened during 1986–92 had confirmed congenital toxoplasmosis. Fifty appeared normal at birth, and in these infants the infection had been diagnosed by screening alone. However, 19 of 48 evaluable infants (40%) who appeared normal on routine examination had evidence of retinal and/or central nervous system disease. Treatment was provided to all the infected infants, and after one year of therapy only one of the children (2.2%) had a neurologic deficit. The laboratory and personnel cost of screening 100,000 babies and following infected babies was estimated to be \$30,000 per infant identified [5]. However, this approach has several important drawbacks: first, the immature immune system of the fetus frequently fails to mount an antibody response to *Toxoplasma* antigens. Second, the sensitivity and specificity of the commercial kits for IgM in neonates is not sufficient, as mentioned above. As a result, infected babies might be missed, or non-infected infants might be falsely diagnosed with congenital infection. In the Danish study the false positive rate was 0.2 per 1,000 deliveries [5]. In a recent study from Poland [13], 4 of 19 infants (20%) with a positive IgM at birth had false positive results and it had taken several months to clarify the correct diagnosis. This implies unnecessary and more expensive confirmatory tests, or even unwanted prolonged and dangerous therapy. Third, with screening at birth the opportunity for prenatal therapy is lost. Finally, no cost-benefit studies have been performed to establish the necessity of this approach.

The second option, which is probably the most sensitive approach but is also the most time-consuming and expensive, is antenatal screening. Such screening programs were implemented in France and Austria in 1975–76 due to the high prevalence of congenital toxoplasmosis in these countries, and led to a sharp decline in the incidence of the disease. Pregnant women are screened for *Toxoplasma* antibodies at their first parental visit. Women who are found to be seronegative are retested at least once every trimester until birth. They are also informed about prevention methods during pregnancy [3]. If seroconversion is documented, then therapy with spiramycin is offered to the mother. If fetal infection is diagnosed, then therapy with pyrimethamin and sulfadiazine is offered to the mother during pregnancy and to the infant until one year of age. This approach has been shown to reduce the rate of infants born with severe sequelae from 20% to 3.5% [4]. A cost-benefit analysis of *Toxoplasma* screening during pregnancy was conducted in a prospective study in Finland [3], a country with a low incidence of congenital toxoplasmosis. It was found that the

annual cost of congenital toxoplasmosis per pregnancy was \$95 with screening versus \$128 without screening.

In Israel, screening would involve serologic testing of women before the pregnancy, and repeat blood tests every 3 months during the pregnancy in about 50% and 70–80% of the Arab and Jewish women respectively. A diagnosis of primary infection would indicate preventive therapy for the mother. In addition, tests (some of which are dangerous to the fetus) such as polymerase chain reaction of the amniotic fluid for DNA of the parasite should be performed in order to diagnose fetal infection. However, this approach also has several drawbacks that may be significant in Israel. Firstly, with such a low prevalence and the insufficient sensitivity and specificity of the assays, many infected fetuses would either not be diagnosed or mothers would erroneously be found to be acutely infected. A recent mathematical analysis showed that in the USA, by using this approach, 12 normal fetuses would be aborted for every single fetus detected with congenital toxoplasmosis [4].

The third option is targeted screening during pregnancy. This involves serologic evaluation of pregnant women with symptoms and signs suggestive of acute toxoplasmosis or with fetal ultrasound findings compatible with the infection (e.g., hydrocephalus). Once the woman is found to be acutely infected, evaluation of the fetus is obtained by PCR of the amniotic fluid for DNA of the parasite. This is a very specific approach, but like the other approaches mentioned, it has several drawbacks. Firstly, most maternal infections during pregnancy are asymptomatic. Secondly, most infected fetuses would have no pathologic findings on ultrasound. Thirdly, IgM can occasionally linger for months or years. Considering the insufficient quality of the commercial tests, when IgM presents, it is desirable to define more precisely how recently the seroconversion occurred. This is done by conducting more precise and sophisticated tests as mentioned above, or using tests such as PCR for *Toxoplasma* genome in the amniotic fluid. Serology studies are either not standardized or are very costly, and should be done in reference laboratories. Finally, false positive tests in the beginning of the pregnancy (when PCR is not possible) may lead to considerable anxiety on the part of those women who elect to continue the pregnancy, and to unnecessary preventive therapy [4].

Primary preventive measures for acute infection during pregnancy would be more effective than screening and would not cost any money [3,4,18]. A recent study in the USA [15] documented that approximately half the cases of *Toxoplasma* exposure may be due to the eating of contaminated food. Prevention programs can be executed by educating women of childbearing age about minimizing their risk for infection with *Toxoplasma*. Educational interventions assume that increased knowledge results in awareness, which consequently leads to a change in risky behavior and a decline in infection rates. In Israel, where the system of regular follow-up during pregnancy is extremely well developed, information on preventive mea-

asures can be given at every appointment, emphasizing the importance of not eating raw or undercooked meat (particularly in the Arab population in Israel), handling raw meat safely, and washing hands after gardening or changing cat litter boxes [3,4]. A Belgian group [16] recently reported a more than 60% reduction in anticipated seroconversion in a cohort of seronegative pregnant women who were educated to undertake a variety of simple hygienic precautions. Another study in Belgium [17] assessed the effectiveness of educational sessions held in a hospital setting. Baseline data were collected during 1979–82, when no education measures were in effect; this was compared to the period 1983–86 during which education sessions were provided to pregnant women. The intervention was associated with a 34% decrease in *Toxoplasma* seroconversion rates. This study may have considerable relevance to Israel and could lead to a significant decrease in the already low prevalence of congenital toxoplasmosis in this country.

In conclusion, the cost-effectiveness of mass screening for congenital toxoplasmosis has not been proven in countries with a low incidence of toxoplasmosis and congenital toxoplasmosis, like Israel. Thus, until more epidemiologic data as well as the results of cost-benefit studies are available, routine screening for the infection during pregnancy or neonatal screening is not justified at this time. Investigation of women suspected of infection during pregnancy, as well as their fetuses, should be performed on a clinical basis as is done for a suspected infected newborn. Since most childbearing women in Israel are seronegative, primary prevention would be the most effective way by far to reduce the already low prevalence of congenital toxoplasmosis in Israel.

References

1. Boyer KM, McLeod RL. *Toxoplasma Gondii*. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 1st edn. New York: Churchill Livingstone Inc., 1997: 1421–48.
2. Montoye JG, Remington JS. *Toxoplasma gondii*. In: Mandell GL, Bennet JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 5th edn. New York: Churchill Livingstone Inc., 2000: 2858–81.
3. Lopez A, Dietz VJ, Wilson A, Navin TR, Jones JL. Preventing congenital toxoplasmosis. *MMWR* 2000;49(RR02):57–75.
4. Mittendorf R, Pryde P, Herschel M, Williams MA. Is routine *Toxoplasma* screening justified in the United States? Statistical consideration in the application of medical screening tests. *Clin Obstet Gynecol* 1999;42:163–73.
5. Lebech M, Andersen O, Cristensen NC, et al. Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. *Lancet* 1999; 353:1834–7.
6. Guerina NG, Hsu H-W, Cody M, et al. Neonatal serologic screening and early treatment for congenital toxoplasma gondii infection. *N Engl J Med* 1994;330:1858–63.
7. Nishri Z, Zalewski SE, Glucks L, Avni R, Lederer J, Mates A. Prevalence of antibodies *Toxoplasma gondii* in the Tel-Mond area. *Isr J Med Sci* 1993;29:30–2.
8. Flatau E, Nishri Z, Mates A, Qupty G, Reichman N, Raz R.

PCR = polymerase chain reaction

- Seroprevalence of antibodies against *Toxoplasma gondii* among recently immigrating Ethiopian Jews. *Isr J Med Sci* 1993;29:395–7.
9. Raz R, Nishri Z, Mates A, et al. Seroprevalence of antibodies against *Toxoplasma gondii* among two rural populations in Northern Israel. *Isr J Med Sci* 1993;29:636–6.
 10. Nishri Z, Yoshpe-Purer Y, Costin C, Ever-Hadani S, Swartz TA. Toxoplasmosis in Israel: evaluation of laboratory data. *Isr J Med Sci* 1978;14:1039–47.
 11. Franklin DM, Dror Z, Nishri Z. The prevalence and incidence of *Toxoplasma* antibodies in pregnant women. *Isr J Med Sci* 1993;29:285–6.
 12. Liesenfeld O, Press C, Montoya JG, et al. False-positive results in immunoglobulin M (IgM) *Toxoplasma* antibodies tests and the importance of confirmatory testing: the Placenta toxo IgM test. *J Clin Microbiol* 1997;35:174–8.
 13. Cozon CJ, Ferrandiz J, Nebhi H, Wallon M, Peryon F. Estimation of the avidity of immunoglobulin G for routine diagnosis of chronic *Toxoplasma gondii* infection in pregnant women. *Eur J Clin Microbiol Infect Dis* 1998;17:32–6.
 14. Pau M, Petersen E, Paolowski ZS, Szczapa J. Neonatal screening for congenital toxoplasmosis in the Poznan region of Poland by analysis of *Toxoplasma gondii* specific IgM antibodies eluted from filter paper blood spots. *Pediatr Infect Dis J* 2000;19:30–6.
 15. Wilson M, Remington JS, Clavet C, Varney G, Press C, Ware D. Evaluation of six commercial kits for detection of human immunoglobulin M antibodies to *Toxoplasma gondii*. *J Clin Microbiol* 1997;35:311–25.
 16. Foulon W, Naessens A, Derde MP. Evaluation of the possibilities for preventing toxoplasmosis. *Am J Perinatol* 1994;11:57.
 17. Foulon W, Naessens A, Lauwers S, DeMeuter F, Amy JJ. Impact of primary prevention on the incidence of toxoplasmosis during pregnancy. *Obstet Gynecol* 1988;72:363–6.
 18. Roghmann MC, Faulkner CT, Lefkowitz A, Patton S, Zimmerman J, Morris JR Jr. Decreased seroprevalence for *Toxoplasma gondii* in Seventh Day Adventists in Maryland. *Am J Trop Med Hyg* 1999;19:20–5.
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