Editorial

Toxoplasmosis: will the time ever come?

D. A. L. PEDREIRA, M. E. CAMARGO* and P. G. LESER*
Departments of Fetal Medicine and *Immunology, Laboratório Fleury, São Paulo, Brazil

THE ‘INITIAL’ IDEA

Since 1992, aware of the preventive programs established in many European countries to deal with congenital toxoplasmosis, we have been trying to implement such a program in Brazil. We believe that toxoplasmosis is the ideal candidate for routine screening in pregnancy, because not only can we prevent it but we can also treat it. This is why we read with so much interest the papers from two different groups published in The Lancet on the subject.

In the first paper, Dunn et al. analyzed data generated in France on vertical transmission of toxoplasmosis. In France, all pregnant women found to be susceptible to toxoplasmosis at their first antenatal visit are asked to undergo repeat serology every 4 weeks. If seroconversion occurs, spiramycin therapy is instituted and prenatal diagnosis is indicated. If fetal infection is confirmed, sulfadiazine and pyrimethamine therapy are added. The authors found a 29% overall rate of vertical transmission of toxoplasmosis in the population. In addition, the authors used a mathematical model to estimate transmission risks according to the exact gestational age (daily interval) of maternal infection. In the second paper, Lebech et al., in Denmark, compared paired samples of newborn and maternal sera, which were collected and stored in the first trimester. No routine maternal screening was performed during pregnancy in this study. These authors found a 20% vertical transmission rate in their population.

A cursory analysis of both studies may lead readers to the conclusion that obsessively screening and treating the disease (as in France), has the same or possibly a worse effect than doing nothing (as in Denmark). If this is indeed true, should we stop trying to implement such a program, and in the meantime, from a practical point of view, what should we be doing?

COMPARING THE STUDIES

A possible explanation for this difference is the gestational age of maternal seroconversion being different between the studies. In Lebech’s work this parameter is not known, because seroconversion was diagnosed only after birth in all cases. One of the strongest points in Dunn’s work, is that they obtained follow up of the vast majority of pregnancies where seroconversion had occurred, regardless of the gestational age of seroconversion or of submission to prenatal diagnosis. As seroconversion is not a predetermined event, it should have occurred at an equal rate in both studies. Therefore gestational age of seroconversion is not likely to be the explanation for the differences between the studies. However, Lebech’s study confined its analysis to liveborn neonates, excluding all miscarriages, stillbirths and terminations due to congenital infection. This could perhaps explain the lower risk that they observed.

Furthermore, Desmonts and Couvreur, who prospectively analyzed the outcome of toxoplasmosis during pregnancy, found a 7% rate of stillbirth or perinatal death: 5% in the first trimester and 2% in the second. In this same study, the transmission rates found were 14%, 29% and 50% in the first, second and third trimesters, respectively. Interestingly, these are the same rates of vertical transmission found by Dunn et al. In our experience, three out of 10 cases of confirmed maternal toxoplasmosis lead to spontaneous fetal death at 14, 18 and 26 weeks of pregnancy. In these cases, toxoplasma was histologically demonstrated (using immunohistochemistry)
in the placenta but not in the fetuses, suggesting that the placenta was responsible for fetal death. It is possible that if these cases were undiagnosed antenatally, they would have been classified as idiopathic if maternal serologic tests were not routinely performed in such cases.

Another aspect to be pointed out in the work of Dunn et al., is the combination made of the risk of transmission vs. the risk of clinical symptoms in the newborn/child. The authors generate a chart that may mislead counseling, giving the impression that the second trimester is the most dangerous period to acquire the disease, and making the third and first trimesters appear to have almost the same risk. We believe that although the numbers are very close, the degree of impairment, mainly in respect to clinical neurologic outcome (which was not the aim of the evaluation) will be very different. The chances are that no sequelae will be found in the majority of the fetuses infected in the third trimester, while, in contrast, those infected in the first trimester will be severely affected (bilateral blindness, mental retardation)\(^1\). Undoubtedly, the work of Dunn et al.\(^1\) is the best study available to provide counseling on transmission risks, but should these data be used in places where no screening is available? Can it be used in other places where maternal serology repetition is done on a trimester basis?

We have to consider that when screening is not performed, the only opportunity to diagnose maternal infection is in the 10–20% of symptomatic cases. So, about 80% of seroconversion would not benefit from this type of screening. In practice, fetal infection is usually only diagnosed once ultrasonographic features, such as ventriculomegaly, are evident. By this stage, fetal treatment is unlikely to alter the long-term neurological outcome. If maternal serology is repeated in each trimester, spiramicyn or any other treatment will be delayed by 2 months compared to the protocol studied by Dunn et al.\(^1\). It is possible that the delay in starting treatment can affect not only the transmission rate, but also the degree of neonatal sequelae, although this data may not be applicable anywhere other than in France.

**WHAT HAPPENS WHEN NO SCREENING IS PERFORMED?**

In our population, although there is no screening policy, toxoplasmosis is a very important problem. Seropositivity among 1286 pregnant women in São Paulo city was found to be 58.9%\(^6\) and a rough mathematical estimation of the incidence of congenital infection, based on the maternal prevalence found, is 0.8/1000 liveborn babies. Diniz (unpublished data, 1998) found 1.7% prevalence of the congenital infection among 190 low birth weight infants in the metropolitan area of the same city (in a non-referral hospital). Among infants born in the nursery of the University of São Paulo between May 1993 and April 1994 (not a referral center for toxoplasmosis at that time), we found two cases of congenital toxoplasmosis diagnosed postnatally (after developing clinical symptoms) among 1475 liveborn babies (1.3/1000), in otherwise normal patients,\(^5\)

We know that bilateral chorioretinitis is characteristic of the congenital infection and it has an important impact because of the progressive impairment of vision, ultimately leading to blindness. The ocular sequelae of toxoplasmosis have frequently been reported in Brazil, not only among adults\(^7\),\(^8\), but even in a case of prenatal diagnosis of fetal cataract\(^9\). Preventive measures are difficult to implement and their effectiveness has been difficult to analyze. When we started working on the subject, toxoplasmosis serology was already routinely performed at the start of prenatal care, as part of a ‘TORCH’-like screening. Our attempts to implement a non-mandatory preventive program (based on education measures and repetition of serology) in a university hospital initially recruited only 8.7% of the susceptible patients\(^10\). In an effort to increase this number, we started sending a note, along with the negative results of the serology (susceptible patients), to the obstetricians, recommending the repetition of the serology. With these data we were able to double the number of patients entering the program\(^11\).

Although the majority of susceptible patients were still not receiving adequate counseling, we started to diagnose seroconversion and were able to prenatally treat the infected fetuses.

During this period, we are aware of at least two cases of congenital toxoplasmosis that occurred in the group where no preventive measures were received. Because these mothers did not undergo repeat serology, maternal seroconversions were only diagnosed after fetal/neonatal problems were diagnosed. One fetus had hydramnios and died at 30 weeks' gestation. At postmortem examination, the placenta was responsible for fetal death. It is possible that if the tests had been repeated, the infection could have been detected and treated. The other case occurred in a 36-year-old woman who was infected during the first trimester. We believe that the fetus was infected through the placenta and that the infection was not detected in the second trimester. The latter are probably responsible for the majority of cases diagnosed in the third trimester. The former should be susceptible to toxoplasmosis, received no information about prevention. Not only from a medical point of view, but also from a legal point of view, early diagnosis and treatment in these pregnancies could have avoided this.

So far, most obstetricians not only in Brazil, but in other countries in Latin America (and this may also be the case in other countries around the world), ask for serology at the first prenatal visit but fail to repeat the test during pregnancy. Major side-effects are generated both by misinterpretation of positive IgM as indicating acute disease, and by the non-identification of the true cases occurring beyond the first trimester. The latter are probably responsible for the majority of cases, since vertical transmission in the first trimester is very low\(^3\). In 1991, Joyson et al.\(^12\) determined that acute cases of toxoplasmosis in adults presented low IgG avidity and that this avidity increased with time after infection. So, testing for IgG avidity could help to identify the true acute cases in isolated ‘IgM-positive’ samples\(^13\). Recently, Cozon et al.\(^14\) suggested that if the avidity index is greater than 35%, the acute infection may be dated more than 12 weeks before the sample collection.

Our laboratory is considered to be a referral center in Brazil and we retrospectively analyzed the results of toxoplasmosis serology of 2475 pregnant patients. We found 60 samples (2.4%) to be IgM positive (automated immuno nephelometric assay: Abbott, Axisym, IL, USA). All but one had a low IgM titer (< 4.0 IU/mL) that we believe to be suggestive of residual titer, now detected due to the increased sensitivity of the new laboratory methods. In this group of ‘low IgM-positive’
patients, an IgG avidity index greater than 30% was found in 97.6% of the samples. We believe that pregnant patients (depending on gestational age of first testing) can be reassured if the IgG avidity found is more than 35%. So, less than 3% of initially ‘at-risk women’ will remain eligible for further investigation. However, we have to point out that the small number of ‘probable’ acute infections that we found may be related to the high socioeconomic level of the patients analyzed in this sample.

THE ROLE OF PRENATAL ULTRASOUND
Ultrasound is part of the follow-up protocol of suspected cases even after an invasive diagnostic procedure has been carried out, because of the possibility of false-negative results or treatment failure. Infected fetuses mainly present ventriculomegaly, intracranial calcifications, chorioretinitis, and hepatosplenomegaly. Ultrasound can easily diagnose hydrocephaly but all the other features may be difficult to detect reliably. For instance, we have detected splenomegaly in six cases of fetal infection and in all but one, hydrocephaly was also found. In this one fetus (submitted to prenatal treatment) splenomegaly was the only associated finding (Figure 2) and hydrocephaly has never developed, suggesting that this may be an early isolated sign of fetal infection.

Termination of the pregnancy, in countries where it is allowed, is usually offered when fetal prognosis is considered to be very poor. In toxoplasmosis, this is the case when hydrocephaly is prenatally detected and, in our opinion, when a cataract is present. We have to be aware that both findings can appear late in pregnancy, being the sequelae of the previous inflammatory process. Thus a late termination may be an option. In all our prenatally diagnosed cases of ventriculomegaly associated with toxoplasmosis we could not detect an increased/increasing head circumference. This suggests that the dilatation of cerebral ventricles, or ventriculomegaly, was most probably caused by an ‘ex vacuum’ mechanism, rather than the ‘classic’ mechanism of aqueductal stenosis.

PREVENTIVE MEASURES AND OTHER RISK FACTORS
Even those who do not advocate routine serologic screening cannot deny the importance of primary prevention by educational measures for the pregnant women. Recently, Cook and coworkers published a very important work on the main risk factors related to seroconversion during pregnancy in European countries. We believe that the major contribution of Cook’s work was to shed light on the importance of bovine meat in the transmission of toxoplasmosis. Although the majority of the known risk factors for acquiring the disease were covered in the study, some questions concerning the proper washing of fruit and vegetables were not addressed, as pointed out by Holliman in his comments on Cook’s work.

In our population, and perhaps elsewhere, another important risk factor seems to be contact with sand pits. Two of the latest seroconversions that we have counseled had taken their

Figure 1 Newborn with congenital toxoplasmosis, looking perfectly normal (a). Suspicion of the infection occurred when hydranencephaly was incidentally diagnosed at 34 weeks of pregnancy (b). Splenomegaly was also present (c).
children to the same sand pit. Both reported that they had seen cats in the pits and a subsequent analysis of the sand revealed toxoplasma oocysts. We also believe that other possible sources of infection should be taken into consideration in such a study, for example, contact with other animals belonging to the ‘cat family’, such as when going to the zoo or to the circus. Having two children myself, I believe that exposure to these risks can be much more frequent in a second pregnancy than in a first one. If this is true, perhaps one would find a significant difference in seroconversion rate according to maternal parity.

IS THERE A DEFINITIVE ANSWER?

If untreated toxoplasmosis leads to fetal death in a certain number of cases, should we screen for it? It seems that only randomized studies involving screening vs. not screening in the same population will answer these questions, but is this ethical? If postnatal treatment has been proved to be effective\cite{Pedreira2001}, should it not start prenatally? Unfortunately, we still rely on data generated in certain developed countries where toxoplasmosis may not be an issue. In Brazil, as may well be the case in many other countries, it is an important problem which requires a solution.

In Brazil, we suffer from a lack of health policies on many issues. The government has to provide healthcare to everybody, but an increasing number of people are seeking private health insurance cover. So, doctors have some freedom to decide what they should be concerned about and patients are gradually being able to pay for their treatment. It is therefore important to rationalize the management of toxoplasmosis, not only in our population, but in other countries where the situation may be similar to ours.

WHAT SHOULD WE DO MEANWHILE?

Since we started working with toxoplasmosis we have kept in our minds words from an article of McCabe and Remington\cite{McCabe1990} entitled ‘Toxoplasmosis: the time has come’. It seems like the time has not yet come, and meanwhile we are left to deal with patients. In our laboratory, every pregnant woman found to be susceptible to toxoplasmosis from the serology results, is immediately provided with a list of primary prevention measures to be taken (Table 1). In addition, we strongly advise their doctors to repeat their serology at 20 and 30 weeks of gestation. However, if the IgM is found to be positive in this first maternal sample, we automatically test it for IgG avidity. If the IgG avidity is more than 30% and the gestational age at time of testing is less than 12 weeks (in the absence of clinical symptoms or risk factors) it is likely that the outcome will be good so nothing other than routine monitoring is necessary.

We are aware that toxoplasmosis is part of routine serologic TORCH screening not only in Brazil, but in many other countries. Initial serology ends up being performed but usually no further preventive measures are recommended. In this way we are left to deal with the problem of ‘IgM positive’

Table 1 Preventive measures to avoid toxoplasmosis

<table>
<thead>
<tr>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid eating raw or undercooked meat (of any origin) or eggs.</td>
</tr>
<tr>
<td>Avoid contact of raw meat with mucous of the mouth and eyes.</td>
</tr>
<tr>
<td>Avoid contact with soil, especially in sand pits.</td>
</tr>
<tr>
<td>Wash fruits and vegetables before eating.</td>
</tr>
<tr>
<td>Avoid contact with cats and other feline feces. If this is not possible, dispose of feces daily and feed cats with well cooked meat.</td>
</tr>
</tbody>
</table>

Figure 2 Newborn with congenital toxoplasmosis, looking perfectly normal. Splenomegaly was prenatally detected (b). Maternal seroconversion was diagnosed at 31 weeks and the fetus was treated. Hydrocephaly never developed. The computer tomography scan at birth was normal.
Editorial

(seldom meaning acute infection), when the majority of congenital toxoplasmosis babies probably arise from maternal infections acquired after the first-trimester test. In conclusion, we strongly believe that susceptible pregnant patients need to be educated on how to avoid the infection, but what we want to emphasize is that there is no point in having the initial serology done without repeating it.

REFERENCES