 International Journal of Epidemiology 2001;**30**:1309–1313

Effect of prenatal treatment on the risk of intracranial and ocular lesions in children with congenital toxoplasmosis

L Gras, RE Gilbert, AE Ades and DT Dunn

Background Hydrocephalus, intracranial calcification and retinochoroiditis are the most common manifestations of tissue damage due to congenital toxoplasmosis, but the effect of prenatal treatment on these outcomes is unclear. We aimed to determine the effect of prenatal treatment for toxoplasmosis on the risk of intracranial and ocular lesions in congenitally infected children at 3 years of age.

Methods A cohort of mothers identified during pregnancy with toxoplasma infection and their 181 liveborn children with confirmed congenital toxoplasmosis was retrospectively analysed to determine the presence of intracranial and ocular lesions. As few women are not treated, we compared the effects of the treatment potency (pyrimethamine-sulfadiazine versus spiramycin or no treatment), and the timing of treatment, on the risks of intracranial lesions, time to detection of ocular lesions, and detection of any lesions (intracranial or ocular) by 3 years of age. Analyses took account of the gestation at maternal seroconversion.

Results There was no evidence for an effect of pyrimethamine-sulfadiazine on intracranial, ocular or any lesions by 3 years: odds ratio (OR) for any lesions 0.89 (95% CI : 0.41, 1.88). There was no evidence of an effect of delayed treatment on ocular lesions (hazard ratio = 0.69, 95% CI : 0.28, 1.68) or any lesions by 3 years of age (OR = 0.44, 95% CI : 0.16, 1.19).

Conclusions Our study failed to detect a beneficial effect of early or more potent anti toxoplasma treatment on the risks of intracranial or ocular lesions in children with congenital toxoplasmosis. However, larger, prospective studies, which determine the effect of prenatal treatment on long-term developmental outcomes are required to justify changes in clinical practice.

Keywords Congenital toxoplasmosis, prenatal treatment, intracranial calcification, retinochoroiditis

Accepted 24 May 2001

The aim of prenatal treatment for infection with *Toxoplasma gondii* is to prevent neurological or visual impairment in infected children either by preventing mother to child transmission of infection, or, once fetal infection has occurred, by limiting cell damage caused by the parasite.[1,2,pp.173–75] In this report, we present results on the effect of prenatal treatment on lesions attributable to parasite-induced cell damage in children with confirmed congenital toxoplasmosis. The lesions most commonly associated with congenital toxoplasmosis are intracranial calcification or hydrocephalus, which are usually detected during infancy, and retinochoroiditis, which may appear at any age.[2] Intracranial and/or ocular lesions were detected before school age in 33% (28/85) of congenitally infected children followed in three population-based cohort studies.[3–5] Of the 28 with lesions, 3 (4%) had severe neurological impairment. Retinochoroidal lesions have been reported in 16% (14/85) children at 1–6 years old,[3–5] of whom up to half may have permanent visual impairment, due to the size of the lesion and involvement of the macular area.[3–6] Information is lacking on the risk of developmental impairment in children with intracranial or ocular lesions. However, many appear to develop normally[6,7] and a small study comparing 17 congenitally infected children and their siblings raises the possibility that impairment may be worse in those with ocular than intracranial lesions (R Eaton, New England Neonatal Screening Program, personal communication).

The effect of prenatal treatment for toxoplasmosis on intracranial or ocular lesions is uncertain. In a study of 144 consecutive

Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London, UK.

women referred to five fetal medicine centres, including 64 with infected children, Foulon *et al.*[8] found a reduction in the risk of lesions at 1 year of age in children born to women given any prenatal treatment compared with those not treated (odds ratio [OR] = 0.3; 95% CI : 0.10, 0.86). However, this study and a case-control study of 103 infected children,[9] found no evidence for an effect of the more potent regimen of pyrimethamine-sulfadiazine compared with spiramycin alone. Both studies endeavoured to account for the effect of gestation at maternal infection[10] but failure to exclude women referred due to fetal abnormalities may have overestimated the risk of lesions in untreated women.

We investigated the effect of prenatal treatment on the risk of signs in a cohort of children with congenital toxoplasmosis born to infected women identified in Lyon, France. As few women received no treatment, we examined whether the risk of lesions was related to the potency of treatment used or to the interval between maternal seroconversion and the start of treatment.

Methods

Patients

The study is based on liveborn children with congenital toxoplasmosis of women who were prospectively identified with toxoplasma infection by the toxoplasma reference laboratory in Lyon, France, between 1987 and 1995. The study methods have been described elsewhere.[10,11] Diagnosis of maternal infection was based on: (a) detection of seroconversion (change from negative to positive specific IgG antibodies); or (b) detection of IgM specific antibodies and, low IgG avidity (<35%), and/or rising specific IgG titre in women who were IgG positive at the first prenatal test. We excluded women referred for suspected fetal infection or abnormality based on scrutiny of referral letters or non-sequential dates for detection of maternal infection, fetal infection or fetal abnormalities. Spontaneous fetal losses or terminations were excluded from the analysis as fetal investigations for lesions (ultrasound or autopsy) were not routinely performed.

Prenatal treatment

After confirmation of infection, women were prescribed spiramycin (9×10^6 units/day) until delivery. If fetal diagnosis was positive, or maternal infection was acquired after 32 weeks, treatment consisted of pyrimethamine (50 mg/day) and sulfadiazine (3 g/day) alternating 3-weekly with spiramycin until delivery (subsequently referred to as pyrimethamine-sulfadiazine). Women with confirmed fetal infection and evidence of intracranial calcification or hydrocephalus on fetal ultrasound were offered termination.

Follow-up

Paediatric examinations were scheduled during the neonatal period, at 2, 5, 8, and 12 months of age, and annually thereafter, or until congenital infection had been excluded. At each visit, the child was examined for retinochoroidal lesions by direct ophthalmoscopy, usually after dilation of the iris, and a blood sample was taken for serology testing. Infants underwent cranial ultrasonography or radiography or both. The dates at which intracranial calcification, hydrocephalus or the first ocular lesion was first detected or the date of the last negative examination was recorded for analysis. We did not analyse the effect of treatment on recurrence of lesions or on the size or site of lesions.

Congenital toxoplasmosis was diagnosed if there was persistence of specific IgG antibodies beyond 12 months of age. Absence of congenital toxoplasmosis was based on a decline in IgG specific antibody beyond detectable levels after discontinuation of treatment. All mother-child pairs in which infection status was unknown were excluded from the analysis.

Postnatal treatment

Neonates with suspected infection were prescribed pyrimethamine (3 mg/kg/3 days) and sulfadiazine (75 mg/kg/day) for 3 weeks, followed by spiramycin (0.375×10^6 units/kg/day) for 2–5 weeks, followed by pyrimethamine (6 mg/kg/10 days) and sulphadoxine (125 mg/kg/10 days) with folinic acid for at least 12 months. All other infants received spiramycin alone pending further evidence of congenital infection status.

Analysis

We investigated the effect of prenatal treatment in two ways. First, we compared the risk of lesions in children born to women treated with spiramycin with those treated with pyrimethamine-sulfadiazine or not treated. We hypothesized that pyrimethamine-sulfadiazine would be more effective in reducing the risk of lesions because it reaches higher levels in fetal blood and, in contrast to spiramycin, is able to penetrate the blood brain barrier.[12] We conducted separate analyses of the effect of treatment on the risks of intracranial and ocular lesions and on any lesions (intracranial or ocular) detected by 3 years of age (follow-up was complete for 95% of the person years of follow-up to 3 years of age). Second, we compared the risk of intracranial, ocular or any lesions in children born to women prescribed any treatment within 4 weeks of estimated seroconversion with those treated 4 or more weeks after seroconversion or not treated.

We used a statistical model, previously described[10,11] to take account of the effect of gestation at seroconversion and the interval between seroconversion and treatment (defined as treatment delay) on the risk of lesions. For women who were IgG positive at the first prenatal test, we assumed that seroconversion occurred between conception and the first positive test.

In the analyses of the risk of intracranial lesions and of any lesion by age 3, we assumed that the effects of treatment and gestational age at seroconversion were additive on a logistic scale. We used a Weibull model to analyse the effect of treatment on the time to first detection of the first ocular lesion and assumed that the hazard was proportional according to treatment categories and gestation at seroconversion. Kaplan-Meier estimates were used to determine the proportion of children without ocular signs according to year of age. The association between the presence of ocular and intracranial lesions was assessed using Fisher's exact test.

Results

Mother to child transmission of infection occurred in 194 of the 704 infected pregnancies with complete data (Figure 1, preceding paper[11]), of which 181 resulted in a live birth. Of the 13 non-live births, 8 fetuses were terminated after 22 weeks, 5 due to hydrocephalus or ventricular dilatation on ultrasound

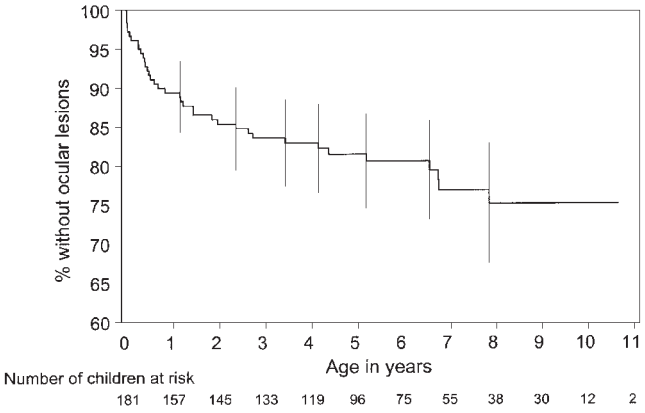

Figure 1 Time till detection of first retinochoroidal lesion in 181 children with congenital toxoplasmosis

Vertical lines represent 95% confidence intervals.

scan: one also had retinochoroidal lesions detected at autopsy. Five fetuses spontaneously aborted or were stillborn, one immediately after cordocentesis at 30 weeks gestation. All analyses presented are based on the 181 congenitally infected liveborn children.

Prenatal treatment consisted of pyrimethamine-sulfadiazine in 70/181 women (39%), spiramycin alone in 89/181 women (49%), and 22/181 (12%) were not treated. The estimated median interval between seroconversion and the start of treatment with pyrimethamine-sulfadiazine was 7 weeks (interquartile range [IQR] 4–10 weeks), and for spiramycin, 4 weeks (IQR 2–7 weeks).

All 181 infected children were treated postnatally. In 177 children, treatment was started within 2 months of birth. All but four children were prescribed pyrimethamine-sulfadiazine and/or pyrimethamine-sulphadoxine. The median age when treatment was stopped was 22 months (IQR 17 months–28 months).

Intracranial and ocular lesions

Hydrocephalus was detected after birth in two children: one also had intracranial calcification; the other died at 8 days of age with hepatitis and disseminated intravascular coagulation after delivery at 34 weeks gestation, following maternal seroconversion between 15 and 22 weeks and prenatal treatment with spiramycin. Intracranial calcification was reported in a total of 17/181 (9%) children. None of the lesions in liveborn children were detected prenatally. In 14 children, the first skull X-ray or cranial ultrasound after birth revealed intracranial calcifications. In one child, intracranial calcification was suspected at birth but not confirmed until the next radiological examination at 3 years old. Two children had normal skull X-rays and ultrasound examinations after birth but intracranial calcification was detected on CT scan when they were re-examined, due to epilepsy, at 2 and 3 years of age.

Retinochoroidal lesions were detected in 37 children after a median follow-up of 6 years 5 months. Figure 1 shows that 7/181 (4%) children had lesions detected during the first month of life, 16 (9%) by 6 months, 19 (11%) by 12 months, 29 (16%) by 3 years, 32 (19%) by 5 years and 36 (23%) by 7 years. Overall, 21/181 children were not completely followed up to 3 years. Follow-up was complete for 95% (516/543) of the total person years up to age 3.

Hydrocephalus, intracranial calcification, and/or ocular lesions were detected by 3 years of age in 38/181 (21%) liveborn children. Ocular lesions were more common in children with intracranial calcification (9/17, 53%) than in children without intracranial calcification (21/164, 13%; $P = 0.0015$).

Effect of type of treatment

There was no evidence that the risk of intracranial lesions (hydrocephalus or intracranial calcification) was reduced in children born to mothers prescribed pyrimethamine-sulfadiazine compared with those prescribed spiramycin alone (adjusted OR = 0.90, 95% CI : 0.29, 2.64) and similarly for untreated mothers compared with those prescribed spiramycin (adjusted OR = 1.04, 95% CI : 0.05, 8.13) (Table 1). Second, there was no evidence that women prescribed pyrimethamine-sulfadiazine were less likely to have children who developed ocular lesions at any age compared with women prescribed spiramycin alone (adjusted hazard ratio = 1.13, 95% CI : 0.56, 2.47). We estimated that if the mother seroconverted at 24 weeks gestation and gave birth to an infected child, the risk of ocular lesions by age 3 years was 15.9% given spiramycin alone, and 17.7% given pyrimethamine-sulfadiazine treatment prenatally: estimated difference—1.8%, (95% CI : –12.7, 8.7%). Finally, we found no evidence that the type of prenatal treatment had an effect on the risk of any lesions by age 3 years (adjusted OR associated with pyrimethamine-sulfadiazine compared with spiramycin = 0.93, 95% CI : 0.42, 2.04).

Effect of treatment delay on clinical signs

The distribution of mother-child pairs, according to type of lesions, estimated treatment delay and gestation at seroconversion is shown in Figure 2. An estimated 40% (72/181) of women were treated within 4 weeks after seroconversion, 34% (58/181) were treated between 4 and 8 weeks, and 16% (29/181) after 8 weeks or more. Of the 22 women who were not treated, postnatal treatment was started within the first three weeks of

Table 1 Effect of prenatal treatment on intracranial and ocular lesions in children with congenital toxoplasmosis

Treatment regimen	Intracranial calcification or hydrocephalus (n = 17) Adjusted odds ratio (95% CI)	Retinochorioditis (n = 37) Adjusted hazard ratio (95% CI)	Any lesion by age 3 years (n = 38) Adjusted odds ratio (95% CI)
Spiramycin alone (n = 79)	1.0	1.0	1.0
Pyrimethamine-sulfadiazine (n = 70)	0.90 (0.29, 2.64)	1.13 (0.56, 2.47)	0.93 (0.42, 2.04)
No treatment (n = 22)	1.04 (0.05, 8.13)	1.29 (0.35, 3.83)	1.45 (0.35, 5.16)

Note: all analyses are adjusted for gestation at seroconversion.

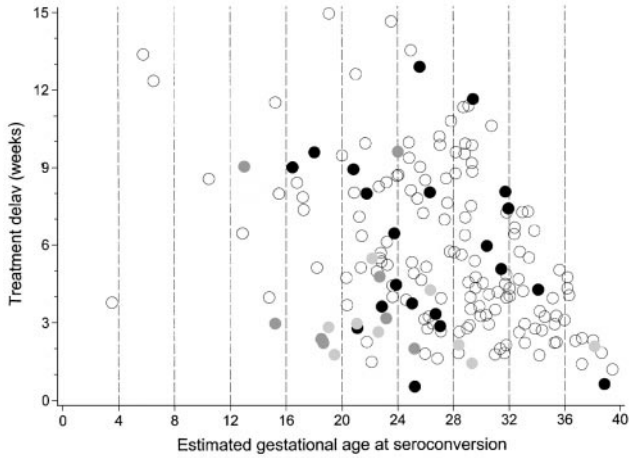

Figure 2 Estimated gestational age at seroconversion and treatment delay according to type of lesion

Dark grey dots = both ocular and intracranial lesions, black dots = ocular lesions by age 3, light grey dots = intracranial lesions and transparent dots = no lesions detected. Treatment delay is plotted against gestation at seroconversion. We assumed that for untreated women, treatment of the child started at delivery. Both measures are based on the estimated date for seroconversion, which was a weighted mean of all possible dates for each woman (weighted by the probability of seroconversion).

life in 19 children, after 1½ months in two and after 3 months in one.

Mothers who gave birth to children with intracranial lesions were significantly more likely to have seroconverted earlier in pregnancy (OR per week of gestation = 0.90, 95% CI : 0.84, 0.97), whereas we did not detect a significant effect of gestation at seroconversion on the risk of ocular lesions (OR = 0.97, 95% CI : 0.93, 1.02).

There was no evidence that delayed treatment had a significant effect on the time to detection of ocular lesions (adjusted hazard ratio for treatment after 4 weeks/no treatment compared with treatment within 4 weeks of seroconversion = 0.69, 95% CI : 0.28, 1.68) or on the risk of any lesions by 3 years of age (adjusted OR = 0.44, 95% CI : 0.16, 1.19).

As treatment may have an effect on mother to child transmission, we determined the overall effect of early (within 4 weeks of seroconversion) compared with delayed or no treatment on the risk of lesions by 3 years of age in infected and uninfected children born to seroconverting women (see preceding paper[11]). The adjusted OR for any lesion at 3 years associated with delayed or no treatment compared with early treatment was 0.63 (95% CI : 0.24, 1.58).

Discussion

We have analysed the largest reported cohort of children with congenital toxoplasmosis, taking care to minimize selection bias due to women with affected fetuses, and taking account of the effect of gestation at maternal seroconversion on the risk of lesions.[10] We found no evidence that prenatal treatment with pyrimethamine-sulfadiazine compared with spiramycin reduced the risk of intracranial or ocular lesions although the 95% CI included both beneficial and harmful effects. There was also no evidence that spiramycin compared with no treatment reduced the risk of intracranial or ocular lesions but due to the small sample size of the untreated group, the power to detect a significant difference between spiramycin and untreated women is low. We also found no evidence that delayed treatment (after 4 or more weeks after seroconversion) or no treatment, reduced the risk of clinical signs by 3 years of age, compared with early treatment (within 4 weeks of seroconversion).

Unexpectedly, the risk of intracranial lesions was significantly reduced in children born to women treated after a delay or not treated at all. Children born to women treated after 4 or more weeks or not treated had a significantly lower risk of intracranial lesions, than for women treated within 4 weeks of seroconversion (adjusted OR = 0.08, 95% CI : 0.01, 0.45). This result may have occurred by chance and is not confirmed by preliminary findings from a larger, prospective European Multicentre Study on Congenital Toxoplasmosis (EMSCOT, unpublished data, R Gilbert). We also considered alternative explanations. First, abnormal fetal ultrasound findings may have led to prompt treatment. After re-checking all patient files, we found no cases of suspected fetal ultrasound abnormalities prior to diagnosis of maternal infection. Second, we investigated whether maternal symptoms of infection could be associated with early treatment and an increased risk of clinical signs but found no evidence of an association: 5% (11/181) of women reported symptoms, of whom one gave birth to a child with signs. A third possible explanation for the reduced risk of intracranial lesions with delayed or no treatment is that early treatment with pyrimethamine-sulfadiazine suppresses the bone marrow[2,p.227] and compromises the maternal and/or fetal immune responses that limit parasite-induced cell damage.[13–15] Our results need to be investigated in more powerful studies that can analyse the effect of early versus delayed treatment according to treatment type.

The lack of evidence for an effect of the more potent regimen of pyrimethamine-sulfadiazine compared with spiramycin alone or no treatment, may be due to treatment after encystment of the parasite has occurred. Once *T. gondii* tachyzoites have crossed the placenta, transformation to the bradyzoite form can occur within days,[16] probably due to stresses caused by the humoral and cell mediated immune responses.[17] Neither spiramycin nor pyrimethamine-sulfadiazine is effective against the encysted, bradyzoite form of the parasite, although experimental studies show that both are effective against the free tachyzoite form.[12] As treatment is always given some time, often weeks, after maternal antibodies develop, it may be given after encystment of the parasite. Due to limitations of sample size and the fact that few women receive pyrimethamine/sulfadiazine immediately after detection of maternal seroconversion, we could not investigate the effects of timing of different types or dosages of treatment.

We found a significant effect of gestation at maternal seroconversion on the risk of intracranial lesions, but a less marked effect on the risk of ocular lesions. These findings may reflect differing immune responses at the two sites resulting in different patterns of lesion development.[17,18]

Conclusions

Our study failed to detect a beneficial effect of prenatal treatment on the risk of clinical signs in infected children. Although

ours is the largest study to date to address this question, the confidence intervals for the effects of different types of treatment are wide. Consequently, we cannot exclude potentially beneficial or harmful effects. The significant finding of a beneficial effect of delayed treatment on intracranial lesions may be due to chance and requires confirmation by further studies. A further concern is the lack of information on the association between intracranial lesions and subsequent developmental impairment. Larger, prospective studies, which determine the effect of prenatal treatment on long-term developmental outcomes are therefore required to justify changes in clinical practice.

Acknowledgements

The study was funded by The Wellcome Trust and by the European Commission BIOMED programme (BMH4-CT98–3927). We thank the staff of Laboratoire de Parasitologie et de Pathologie Exotique, Hôpital de la Croix Rousse, Lyon, for help with data collection and Eskild Petersen for helpful comments on drafts of the report and facilitating the collaboration. We thank Martine Wallon and Francois Peyron for providing the data and for contributing to the design, execution and interpretation of the study. The conclusions in this paper do not reflect the opinions of the clinicians in the department which provided the data.

References

[1] Jeannel D, Costagliola D, Niel G, Hubert B, Danis M. What is known about the prevention of congenital toxoplasmosis? *Lancet* 1990;**336:** 359–61.

[2] Remington JS, McLeod R, Desmonts G. Toxoplasmosis. In: Remington JS, Klein J (eds). *Infectious Diseases of the Fetus and Newborn. 4th Edn*. Pennsylvania: WB Saunders, 1995, pp.140–267.

[3] Guerina NG, Hsu HW, Meissner HC *et al*. Neonatal serologic screening and early treatment for congenital Toxoplasma gondii infection. The New England Regional Toxoplasma Working Group. *N Engl J Med* 1994;**330:**1858–63.

[4] Lebech M, Andersen O, Christensen NC *et al*. Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. *Lancet* 1999;**353:**1834–37.

[5] Conyn-van-Spaedonck MAE. *Prevention of Congenital Toxoplasmosis in the Netherlands* (Thesis). National Institute of Public Health and Environmental Protection (Netherlands), ISBN 90–9004179–6. 1991.

[6] Koppe JG, Loewer Sieger DH, de Roever Bonnet H. Results of 20-year follow-up of congenital toxoplasmosis. *Lancet* 1986;**i:**254–56.

[7] Berrebi A, Kobuch WE, Bessieres MH *et al*. Termination of pregnancy for maternal toxoplasmosis. *Lancet* 1994;**344:**36–39.

[8] Foulon W, Villena I, Stray-Pedersen, B *et al*. Treatment of toxoplasmosis during pregnancy: a multicentre study of impact on fetal transmission and children's sequelae at age 1 year. *Am J Obstet Gynecol* 1999;**180:**410–15.

[9] Couvreur J, Thulliez P, Daffos F *et al*. *In utero* treatment of toxoplasmic fetopathy with the combination pyrimethamine-sulfadiazine. *Fetal Diagn Ther* 1993;**8:**45–50.

[10] Dunn D, Wallon M, Peyron F, Petersen E, Peckham CS, Gilbert RE. Mother to child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet* 1999;**353:**1829–33.

[11] Gilbert RE, Gras L, Wallon M, Peyron F, Ades AE, Dunn, D. Effect of prenatal treatment on mother to child transmission of *Toxoplasma gondii*: a cohort study of 554 mother-child pairs in Lyon, France. *Int J Epidemiol* 2001;**30:**1303–08.

[12] Derouin F. Drugs effective against *Toxoplasma gondii*. Present status and future perspective. In: Amboise-Thomas P, Petersen E (eds). *Congenital Toxoplasmosis. Scientific Background, Clinical Management and Control*. Paris: Springer Verlag, 2000, pp.95–110.

[13] McLeod R, Dowel M. Basic immunology: fetus and the newborn. In: Amboise-Thomas P, Petersen E (eds). *Congenital Toxoplasmosis. Scientific Background, Clinical Management and Control.* Paris: Springer Verlag, 2000, pp.37–68.

[14] Alexander J, Roberts CW, Walker W, Reichmann G, Hunter CA. The immunology of *Toxoplasma gondii* infection in the immune-competent host. In: Amboise-Thomas P, Petersen E (eds). *Congenital Toxoplasmosis. Scientific Background, Clinical Management and Control.* Paris: Springer Verlag, 2000, pp.69–82.

[15] Dammann O, Leviton A. Infection remote from the brain, neonatal white matter damage, and cerebral palsy in the preterm infant. *Semin Pediatr Neurol* 1998;**5:**190–201.

[16] Luder CGK, Giraldo Velasquez MA, Sendtner M, Gross U. *Toxoplasma gondii* in primary rat CNS cells: differential contribution of neurons, astrocytes, and microglial cells for the intracerebral development and stage differentiation. *Exp Parasitol* 1999;**93:**23–32.

[17] Roberts F, McLeod R. Pathogenesis of toxoplasmic retinochoroiditis. *Parasitol Today* 1999;**15:**51–57.

[18] Brezin AP, Kasner L, Thulliez P *et al*. Ocular toxoplasmosis in the fetus. immunohistochemistry analysis and DNA amplification. *Retina* 1994; **14:**19–26.

 International Journal of Epidemiology 2001;**30**:1314–1315

Commentary: Little evidence of effective prenatal treatment against congenital toxoplasmosis—the implications for testing in pregnancy

Anne Eskild and Per Magnus

Testing for antibodies against *Toxoplasma gondii* in pregnancy is routinely offered in some countries. However, no randomized controlled trials of the effect of treatment have been performed, and the question of whether testing in pregnancy should be encouraged rests on evidence from observational studies. Two such studies are presented in this issue. The first investigated the effect of timing and type of treatment on the risk of vertical transmission.[1] The authors hypothesize that the lack of effect in their study is explained by rapid transmission to the fetus after maternal infection, implying that the initiation of treatment comes too late.

The other study estimates the impact of timing and type of treatment on the risk of intracranial and ocular lesions in congenitally infected children at 3 years of age.[2] Even after controlling for the length of gestation at maternal infection, they found a paradoxical effect of treatment. A long interval from seroconversion to treatment lowered the risk of intracranial lesions, whereas the opposite would be expected. The interval seemed to have no impact on the risk of ocular lesions and the type of treatment did not seem to influence the risk of congenital damage. The authors state that their results provide no evidence that prenatal screening is beneficial.

The French Studies in Context

The finding of no treatment effect on the transmission rate is in agreement with a recent European multicentre study including 144 infected women,[3] and with systematic literature reviews.[4,5] However, estimates of transmission rates vary widely. In the present study,[1] the proportion of infected children was 28%, while it was 19% in a large population-based Danish study.[6] In the multicentre study,[3] the transmission rate varied from 30% to 73% between centres, with an overall value of 44%. This variability raises issues of inter-study differences in selection of cases or differences in laboratory methods.

The finding in the second study[2] that treatment has no beneficial effect on sequellae is in contrast to the results from the multicentre study,[3] where a significant, protective effect of treatment is reported. The studies differ in their analytical approach. The study by Gras *et al*.[2] includes only outcomes in children where transmission has occurred (i.e. the children who are at direct risk of sequellae), while the multicentre study[3] includes children of all seroconverting women in the analysis (the outcome is a combination of risk of transmission and risk of sequellae given transmission). If the latter study[3] had limited the analysis to children under direct risk, it appears from inspection of the reported data that the protective effect would have been smaller and insignificant, although this cannot be directly judged since the distribution of gestational age at infection (the main confounder) is not presented by treatment group. A major problem with all the observational studies is the selection of patients to treatment, and given treatment, the selection to short or long time intervals before treatment starts.

Implications for Testing in Pregnancy

The observational studies discussed above do not provide convincing evidence for beneficial effects of prenatal treatment of toxoplasmosis. Treatment in pregnancy should, in our opinion, be regarded as experimental, and only be performed as part of carefully conducted randomized trials.

Even if there were a beneficial effect of treatment in pregnancy, there may not be an overall positive effect of screening. The effect of screening depends on the magnitude of the health problem, the estimated treatment effect, but also on the compliance to the screening programme and the treatment.[5] Also, possible side effects of treatment must also be considered, as discussed by Gras *et al*. on the basis of their findings.[2] Pyrimethamine is a folic acid antagonist. The use of folic acid antagonists in pregnancy has been associated with increased risk of neural tube defects.[7] Termination of pregnancy with a healthy fetus and complications to invasive prenatal diagnosis are other important potential side effects. In addition to the economic costs and the use of limited health resources, which traditionally have been in focus when debating screening initiation, the psychological aspects have come increasingly into focus.[8] Initial false positive diagnoses are common when screening for disorders of low prevalence. Both false and verified positive diagnoses may cause anxiety in the mother and her family throughout the pregnancy and reduce the positive expectations for the new child, even though the risk of a severely diseased child is low.

On this background, should one commence health district-randomized controlled trials on the effect of introducing a screening programme of testing in pregnancy? In today's situation, with little evidence of any beneficial effect of treatment, our opinion is no. First, one should document that treatment is effective.

Section of Epidemiology, National Institute of Public Health, PO Box 4404 Nydalen, 0403 Oslo, Norway.

Future Research

We suggest that the effect of prenatal treatment should be tested out using an ordinary double-blind placebo-controlled clinical trial with randomization on an individual basis.

Additionally, better estimates of the burden of disease should be made, including population statistics. How many children in a certain population will suffer from the consequences of congenital toxoplasmosis? The observational studies give little detail as to the degree of disability and illness experienced by these children. Such data are also needed for evaluation of public health actions.

We also suggest that controlled community trials could be performed to estimate the effect of primary prevention directed against established risk factors.[9] Thus, one could randomize health care districts to have intervention or no intervention, where the intervention might consist of detailed advice to women in early pregnancy to modify behaviour with respect to consumption of raw or undercooked meat and unwashed vegetables, and behaviour with respect to contact with cat faeces.

References

[1] Gilbert RE, Gras L, Wallon M, Peyron F, Ades AE, Dunn DT. Effect of prenatal treatment on mother to child transmission of *Toxoplasma gondii*: retrospective cohort study of 544 mother-child pairs in Lyon, France. *Int J Epidemiol* 2001;**30:**1303–08.

[2] Gras L, Gilbert RE, Ades AE, Dunn DT. Effect of prenatal treatment on the risk of intracranial and ocular lesions in children with congenital toxoplasmosis. *Int J Epidemiol* 2001;**30:**1309–13.

[3] Foulon W, Villena I, Stray-Pedersen B *et al*. Treatment of toxoplasmosis during pregnancy: a multicenter study of impact on fetal transmission and children's sequelae at one year of age. *Am J Obstet Gynecol* 1999; **180:**410–15.

[4] Wallon M, Liou C, Garner P, Peyron F. Congenital toxoplasmosis: systematic review of evidence of efficacy of treatment in pregnancy. *Br Med J* 1999;**318:**1511–14.

[5] Eskild A, Oxman A, Magnus P, Bjørndal A, Bakketeig LS. Screening for toxoplasmosis in pregnancy: what is the evidence of reducing a health problem? *J Med Screening* 1996;**3:**188–94.

[6] Lebech M, Andersen O, Christensen NC *et al*. Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. *Lancet* 1999;**353:**1834–37.

[7] Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001;**153:**961–68.

[8] Stewart-Brown S, Farmer A. Screening could seriously damage your health. *Br Med J* 1997;**314:**533–34.

[9] Kapperud G, Jenum PA, Stray-Pedersen B, Melby K, Eskild A, Eng J. Risk factors for toxoplasma infection in pregnancy. Results from a prospective study in Norway. *Am J Epidemiol* 1996;**144:**405–12.

International Journal of Epidemiology 2001;**30**:1315–1316

Commentary: Efficacy of prenatal treatment for toxoplasmosis: a possibility that cannot be ruled out

P Thulliez

In their retrospective cohort study of 554 mother-child pairs, Gilbert *et al*. did not detect a significant effect of prenatal treatment on the risk of vertical transmission of toxoplasmosis.[1] This result is not surprising as there were very few untreated women and the analysis of no treatment versus pyrimethamine-sulphadiazine was restricted to half of the cohort who did not undergo amniocentesis. The confidence interval (0.37–3.03) for the odds ratio (1.06) for no treatment compared with pyrimethamine-sulphadiazine was therefore very wide and could include a doubling in the risk of transmission in untreated women. Thus an absence of evidence of prenatal treatment effect does not exclude a clinically important beneficial effect.

Laboratoire de la Toxoplasmose, Institut de Puériculture, Paris, France.

A further problem is that most of the untreated women were infected during the third trimester of pregnancy. Figure 4 shows that only three women infected before 28 weeks of gestation were not treated. The remaining 28 untreated women were infected after 28 weeks. The effect of treatment in the third trimester cannot be generalized to the whole of pregnancy. Finally, the authors explain their findings by suggesting that vertical transmission occurs soon after infection, during parasitaemia. This hypothesis is not supported by any scientific studies in humans. On the contrary, one study found that the sensitivity of prenatal diagnosis was lower in early than mid pregnancy, suggesting that vertical transmission may be delayed for some women infected in early pregnancy.[2]

In the second report by Gras *et al.*,[3] the authors unexpectedly found no evidence that prenatal treatment with pyrimethamine-sulphadiazine was more effective than spiramycin in reducing

the risks of intracranial or ocular lesions in congenitally infected infants by 3 years of age. A potential explanation for this result is that mothers who transmitted the infection to their fetus soon after infection were more likely to be treated with pyrimethamine-sulphadiazine than mothers infected at the same gestation but in whom transmission was delayed until later in pregnancy. These two groups may not be comparable as fetuses infected earlier in pregnancy have a higher risk of clinical signs. This explanation is suggested by the fact that mothers infected before 32 weeks were only given pyrimethamine-sulphadiazine if the diagnosis of fetal infection was positive (i.e vertical transmission occurred between maternal infection and the date of fetal sampling). Other mothers infected before 32 weeks were treated with spiramycin until delivery, either because the prenatal diagnosis was negative or not attempted. In this latter group, transmission occurred either after amniocentesis or at some unknown time between the date of maternal infection and delivery, that is later during gestation than in the group receiving pyrimethamine-sulphadiazine.

There are two further explanations for the lack of effect of pyrimethamine-sulphadiazine. Firstly, there was a long delay before pyrimethamine-sulphadiazine was started. This was because the study was carried out more than 6 years ago, when mouse inoculation was the standard fetal diagnostic test[4] and pyrimethamine-sulphadiazine treatment would have been delayed for 3–6 weeks until results were known. Today, PCR analysis of amniotic fluid is widespread. Results are available in one day and women with infected fetuses are treated much earlier.[5] Secondly, women in the study given pyrimethamine-sulphadiazine actually received an alternating regimen with spiramycin. The periods of spiramycin treatment may have led to parasitic relapses in fetal tissues, as shown in experimental models.[6] The current treatment policy for women with a positive prenatal diagnosis is to prescribe continuous treatment with pyrimethamine-sulphadiazine until delivery. The data reported by Gilbert *et al.*[1] and Gras *et al.*[3] provide no convincing evidence that this policy should change.

References

[1] Gilbert RE, Gras L, Wallon M, Peyron F, Ades AE, Dunn DT. Effect of prenatal treatment on mother to child transmission of *Toxoplasma gondii*: retrospective study of 554 mother-child pairs in Lyon, France. *Int J Epidemiol* 2001;**30:**1303–08.

[2] Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol* 2001;**97:**296–300.

[3] Gras L, Gilbert RE, Ades AE, Dunn DT. Effect of prenatal treatment on the risk of intracranial and ocular lesions in children with congenital toxoplasmosis. *Int J Epidemiol* 2001; **30:**1309–13.

[4] Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet* 1999;**353:**1829–33.

[5] Hohlfeld P, Daffos F, Costa JM, Thulliez P, Forestier F, Vidaud M. Prenatal diagnosis of congenital toxoplasmosis with a polymerase-chain-reaction test on amniotic fluid. *N Engl J Med* 1994;**331:** 695–99.

[6] Piketty C, Derouin F, Rouveix B, Pocidalo JJ. *In vivo* assessment of antimicrobial agents against *Toxoplasma gondii* by quantification of parasites in the blood, lungs, and brain of infected mice. *Antimicrob Agents Chemother* 1990;**34:**1467–72.