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ARTICLE

Predictors of Retinochoroiditis in Children With Congenital Toxoplasmosis: European, Prospective Cohort Study

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What's Known on This Subject

Twenty percent of children with congenital toxoplasmosis have retinochoroidal lesions by school age. Clinicians lack information on which children are most at risk and need ophthalmic follow-up and whether prenatal and postnatal treatment reduces the risk of ocular disease.

What This Study Adds

Prenatal treatment did not significantly reduce the risk of retinochoroiditis. Children with congenital toxoplasmosis who have no retinochoroiditis in early infancy are at low risk of subsequent lesions and may not justify postnatal treatment and repeated ophthalmic assessments.

ABSTRACT

OBJECTIVE. By school age, 20% of children infected with congenital toxoplasmosis will have ≥1 retinochoroidal lesion. We determined which children are most at risk and whether prenatal treatment reduces the risk of retinochoroiditis to help clinicians decide about treatment and follow-up.

PATIENTS AND METHODS. We prospectively studied a cohort of children with congenital toxoplasmosis identified by prenatal or neonatal screening in 6 European countries. We determined the effects of prenatal treatment and prognostic markers soon after birth on the age at first detection of retinochoroiditis.

RESULTS. Of 281 children with congenital toxoplasmosis, 50 developed ocular disease, and 17 had recurrent retinochoroiditis during a median follow-up of 4.1 years. Prenatal treatment had no significant effect on the age at first or subsequent lesions. Delayed start of postnatal treatment did not increase retinochoroiditis, but the analysis lacked power. Older gestational age at maternal seroconversion was weakly associated with a reduced risk of retinochoroiditis. The presence of nonocular clinical manifestations of congenital toxoplasmosis at birth strongly predicted retinochoroiditis. For 92% (230 of 249) of children with no retinochoroiditis detected before 4 months of age, the probability of retinochoroiditis by 4 years was low, whether clinical manifestations were present or not 8.0%.

CONCLUSIONS. Prenatal treatment did not significantly reduce the risk of retinochoroiditis in this European cohort. If children have no retinochoroiditis in early infancy, the low risk of subsequent ocular disease may not justify postnatal treatment and repeated ophthalmic assessments during childhood. Controlled trials are needed to address the lack of evidence for the effectiveness of postnatal treatment.

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Key Words
congenital toxoplasmosis, retinochoroiditis, prospective cohort, treatment effectiveness

Abbreviations
Ig—immunoglobulin
OR—odds ratio
CI—confidence interval
IQR—interquartile range

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CONGENITAL TOXOPLASMOSIS CAUSES retinochoroidal lesions, which can occur at any time in fetal or postnatal life. The risk of retinochoroiditis rises from 10% in infancy to approximately one third by 12 years of age in children whose infection was identified by screening.[1,2] More than 90% of children with retinochoroiditis have normal vision in their best eye; severe bilateral impairment is rare.[2,3]

Prevention of retinochoroiditis through prenatal and postnatal antitoxoplasma treatment is one of the principal rationales for prenatal and neonatal toxoplasma screening programs operating in Europe, the United States, and South America.[4,5] A recent meta-analysis of all of the available cohort studies of children with congenital toxoplasmosis found no evidence that prenatal treatment reduced the risk of reti-

TABLE 1 **Age at Last Ophthalmic Examination and Occurrence of Retinochoroiditis According to Screening Program in Children With Congenital Toxoplasmosis**

Region and Screening Program	No. of Infected Children	Age at Last Ophthalmic Examination Median (Range), y	No. With Retinochoroiditis (%)	No. of Children With ≥1 Recurrent Lesion (%)		
				≥1	≥2	≥3
Prenatal screening						
France	171	3.8 (0.0–7.1)	26 (15)	10	3	2
Austria/Italy	39	4.4 (0.0–7.5)	8 (21)	4	1	0
Neonatal screening						
Poland/Scandinavia	71	4.2 (0.1–11.5)	16 (22)	7	3	2
Total	281	4.1 (0.0–11.5)	50 (18)	21 (42%)	7 (14%)	4 (8%)

nochoroiditis in infancy.[5] Less is known about the longer-term effects of prenatal treatment on retinochoroiditis. One French cohort study found no evidence for any benefit of timing or the type of prenatal treatment (spiramycin or pyrimethamine-sulfonamide combination) in children followed to school age, but, because virtually all of the women were treated, the effect of treatment versus no treatment could not be examined.[2,6]

The present study compares long-term ocular outcomes in children whose mothers were treated with those not treated during pregnancy. We also provide prognostic information for clinicians counseling parents about their child's risk of developing retinochoroiditis and the need for postnatal treatment and ophthalmic follow-up.

METHODS

Study Population

The original study population consisted of 284 children, of which 3 did not have any ophthalmologic examinations. Thus, 281 children identified prospectively by universal prenatal ($n = 210$) or neonatal screening ($n = 71$) in 6 European countries are included (Table 1). All except 25 of the children enrolled in the Danish Neonatal Screening Study from 1992 to 1996[7] were part of the European Multicenter Study on Congenital Toxoplasmosis for which screening and treatment programs and methods for excluding referred infants have been described in detail elsewhere.[1,8]

Congenital Infection Status and Ophthalmic Outcomes

Classification of congenital infection was based on serologic follow-up to 1 year, as described previously.[8] Ophthalmic examinations were performed after pupil dilatation a median of 2 times during infancy (1–6 examinations) and thereafter annually. Ophthalmologists completed a standard proforma and were asked to use indirect ophthalmoscopy whenever possible. Laterality (right or left), site (posterior pole or periphery), size, and date each retinochoroidal lesion was first detected were recorded. We defined a recurrence as a new lesion that was detected for the first time >1 week after a previous adequate visualization of the retina. At a single examination, ≥1 lesion could be detected in the same eye (termed "multiple lesions").

Determinants of Age at Retinochoroiditis

Gestational Age at Maternal Seroconversion

The gestational age at maternal seroconversion is a surrogate marker for the timing of fetal infection.[8] This variable was included in all of the analyses, because we reasoned that the risk of retinochoroiditis might decrease as fetal immunity matures, a hypothesis supported by a strong inverse association between intracranial lesions and gestational age at maternal seroconversion.[1,5] We imputed the date of maternal seroconversion as either the midpoint between the last negative and first positive maternal immunoglobulin M (IgM) tests for women who had prenatal screening and a positive IgG test at the first IgM test or 14 days before the first positive IgM test for women with a negative IgG test at their first positive prenatal IgM test.[1,5,9]

For children identified by neonatal screening, we used the dates of the first prenatal booking blood sample and birth to define the seroconversion interval and imputed the date of seroconversion using a regression analysis with covariates for IgM status (based on the immunosorbent agglutination assay test and, if not available, the enzyme-linked immunosorbent assay test) and the rank of the IgG titer (based on the Dye test and, if not available, an enzyme-linked immunosorbent assay test) in the child's first postnatal sample.[5] The multiple linear regression model was derived from children identified by prenatal screening and then used to impute the gestational age at maternal seroconversion for children identified by neonatal screening. The regression model was as follows: gestational age at seroconversion in weeks = 33.31272 + 5.65140 * first IgM test (positive/equivalent = 1, negative = 0) − 0.32782 * IgG titer percentile rank + 0.00218 * IgG titer percentile rank squared. Gestational age at seroconversion was weighted in all of the analyses by the reciprocal of the interval between the last negative and first positive test dates or conception and birth if no prenatal tests were performed. Using this method, results for the effect of gestational age at maternal seroconversion on the risk of ocular lesions by 4 years of age (odds ratio [OR]: 0.97; 95% confidence interval [CI]: 0.93–1.00) agreed closely with previous findings for ocular lesions during infancy using the maximum likelihood method in analyses of the same data set (OR: 0.97; 95% CI: 0.94–1.01) and in an individual patient data meta-analysis

of all of the available cohort data sets (OR: 0.97; 95% CI: 0.93–1.00).[1,5]

Treatment

Prenatal testing and treatment regimens varied. France used monthly retesting of susceptible women and spiramycin as the first treatment, whereas Austria used 3-monthly retesting and a pyrimethamine-sulfonamide combination as the first treatment (details reported elsewhere).[8] Mothers were not treated in neonatal screening centers.

To determine the association between the timing of prenatal treatment and age at detection of retinochoroiditis, we compared prenatal treatment started before 4 weeks or ≥4 weeks after maternal seroconversion with no prenatal treatment (4 weeks is close to the median treatment delay for women in France).[1] We also examined the effect of any treatment compared with none and differences in effects among the types of prenatal treatment.

Only limited investigation of the effect of postnatal treatment was possible, because all except 3 of the children received postnatal treatment, all with regimens containing pyrimethamine-sulfonamide. Protocols for the duration of treatment varied from 3 months in Denmark to 24 months in parts of France.[1] Because postnatal treatment can only have an effect if given before retinochoroiditis occurs, we restricted these analyses to children who had a normal ophthalmoscopy after birth.

Clinical Prognostic Markers

Clinicians need to counsel parents about their child's prognosis to make decisions about postnatal treatment and follow-up. We analyzed the effect of demographic variables (maternal age, child's gender, and region defined as France, Scandinavia and Poland, and Austria or Italy), clinical markers in pregnancy (fetal ultrasound results or maternal lymphadenopathy), and clinical manifestations present at or soon after birth (before 4 months old) on the age at first detection of retinochoroiditis. Four months was chosen because virtually all of the initial clinical assessments had been completed by this time. Clinical manifestations in the child were defined in a mutually exclusive hierarchy as follows: serious neurologic findings (seizure, hydrocephaly, or microcephaly); intracranial lesions detected by postnatal ultrasound scan (ventricular dilatation and/or intracranial calcification without serious neurologic findings); lymphadenopathy or hepatosplenomegaly; and no manifestations. The cohort ascertained in Denmark between 1992 and 1996 lacked data on non-ocular clinical manifestations and timing of postnatal treatment and was excluded from these analyses.[7]

Analyses

Descriptive statistics include relative frequencies and percentages for categorical variables. Kaplan-Meier models were fitted to describe the time to first detection of a lesion after birth. If a child had no lesions, censoring occurred at the date of the last ophthalmic examination. The primary analysis used birth as the point after which lesions could be detected (time 0). We compared the effect of prenatal and postnatal determinants on the age at detection of first retinochoroidal lesion using the log-rank test and derived hazard ratios, adjusted for gestational age at maternal seroconversion using Cox proportional hazards regression. The probability of retinochoroiditis and 95% CIs were estimated from the unadjusted survival analyses using 1 minus the estimate of success from the time of the last previous event and corresponding SE. To compare the effect of determinants on the timing and occurrence of recurrent lesions we used the Prentice, Williams, and Peterson total time model for ordered multiple failure times with common effects,[10] which assumes proportional hazards with time-dependent strata for times to each of the ordered k events. A common-effects model was chosen because of limited power (ie, few subjects with 3 or 4 events). All of the multivariate analyses were adjusted for gestational age at maternal seroconversion and weighted by the reciprocal of the interval between the last negative and first positive test dates or birth. Baseline characteristics of those lost to follow-up by 1 year were compared with those with data at 1 year using χ^2 or exact tests for categorical variables and t tests or Wilcoxon rank-sum tests as appropriate for continuous variables. Results were considered statistically significant for $P < .05$.

We used sensitivity analyses, with time 0 redefined as the gestational age at maternal seroconversion, to take into account the fact that infants infected early in pregnancy might develop retinochoroiditis sooner after birth than infants infected in later pregnancy. We also examined the effect of prenatal treatment on retinochoroiditis that occurred for the first time after birth by restricting the analysis to children whose first ophthalmoscopy after birth was normal. To test for possible bias, all of the analyses were repeated for French centers only, because referral bias is expected to be low in France, where compliance with screening is mandated by law.[11] All of the calculations were performed using SAS 9.1.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

The cohort was composed of 284 children with congenital toxoplasmosis. All except 3 of the children had ≥1 ophthalmoscopy examination during a median follow-up of 4.1 years (Table 1). Indirect ophthalmoscopy was used at least once in all of the children and for nearly two thirds (180 of 281 [64%]) of the latest examinations. There was no significant association ($P > .05$) between clinical characteristics and whether ($n = 15$) or not ($n = 163$) the child was lost to follow-up at 1 year.

Forty-nine children had ≥1 retinochoroidal lesion, and in 1 additional child with microphthalmia, cataracts, and vitreous opacities, we assumed that retinochoroiditis was present at birth, although the retina could not be visualized (50 of 281 [18%]). Less than half of the children with retinochoroiditis (21 of 50 [42%]) had ≥1 recurrent lesion, and 4 (8%) had ≥3 recurrences (Table

TABLE 2 **Hazard Ratios for Age at First Detection of Retinochoroiditis and Probability of Retinochoroiditis by 4 Years Old According to Pregnancy and Infant Characteristics**

Characteristic	No. of Children With		Hazard Ratio (95% CI)[a]	Probability of Retinochoroiditis by 4 Years (95% CI), %
	Retinochoroiditis	Congenital Toxoplasmosis		
All children	50	281	—	16.5 (11.9–21.1)
Maternal factors				
Gestational age at seroconversion: per week increase in gestation	50	281	0.97 (0.93–1.00)	—
Early versus late pregnancy				
>20 wk (reference)	38	234	1.0	14.6 (12.4–19.4)
≤20 wk	12	47	2.10 (1.08–4.10)[b]	25.8 (12.4–39.3)
Lymphadenopathy during pregnancy[c]				
None (reference)	38	243	1.0	16.0 (11.0–20.9)
Any	3	13	1.19 (0.32–4.46)	29.5 (0.0–59.6)
Mother's age				
Per year increase in age	50	281	0.99 (0.93–1.05)	—
Maternal age groups				
<30 y (reference)	33	190	1.0	16.5 (10.8–22.2)
≥30 y	17	91	0.98 (0.54–1.78)	16.3 (8.4–24.2)
Region of study				
France (reference)	26	171	1.0	16.2 (10.1–22.3)
Italy/Austria	8	39	1.11 (0.45–2.74)	18.9 (6.2–31.4)
Scandinavia/Poland	16	71	0.76 (0.29–1.98)	16.0 (7.3–24.8)
Prenatal treatment				
Treated versus untreated				
Untreated (reference)	20	103	1.0	15.5 (8.2–22.7)
Treated during pregnancy	30	178	0.83 (0.39–1.79)	17.1 (11.1–23.1)
Treatment delay (treated women only)				
Per week of delay	30	169	0.99 (0.87–1.12)	—
Treatment delay (versus no treatment)				
No treatment (reference)	20	103	1.0	15.5 (8.2–22.7)
<4 wk	18	114	0.82 (0.38–1.79)	15.6 (8.4–22.7)
≥4 wk	12	64	0.84 (0.32–2.20)	19.7 (9.0–30.3)
Type of treatment				
No treatment (reference)	20	103	1.0	15.5 (8.2–22.7)
Spiramycin alone	9	82	0.50 (0.20–1.23)	13.1 (4.9–21.2)
Spiramycin and then P&S	16	58	1.52 (0.67–3.46)	27.3 (14.8–39.8)
P&S	5	38	0.55 (0.17–1.78)	11.2 (0.8–21.6)
Prenatal and postnatal treatment[c]				
Delay to start of prenatal/postnatal treatment				
Per week of delay	41	256	1.00 (0.99–1.01)	—
Age at start of postnatal treatment[d]				
Per week of postnatal age	21	218	1.00 (0.99–1.01)	—
Clinical characteristics of fetus/child				
Gender of child				
Male (reference)	28	152	1.0	15.2 (9.3–21.0)
Female	22	129	1.11 (0.62–1.97)	18.0 (10.7–25.2)
Gestation at birth	50	281	0.95 (0.82–1.10)	—
Term (reference)	41	243	1.0	15.9 (11.0–20.8)
Preterm	9	38	0.98 (0.42–2.31)	18.7 (6.2–31.3)
Fetal ultrasound scan (US)[e]				
Any abnormality				
Normal scan (reference)	29	198	1.0	15.0 (9.6–20.5)
Any abnormality	5	9	6.60 (2.06–21.09)[b]	55.6 (23.1–88.0)
Intracranial calcification/ventricular dilatation				
No intracranial abnormality (reference)	29	202	1.0	14.8 (9.4–20.1)
Intracranial abnormality	5	5	118.29 (21.62–647.22)[b]	1.0 (47.8–1.0)
Clinical manifestations in early infancy (exclusive hierarchy before 4 mo)[c]				
Specific manifestations				
None (reference)	26	221	1.0	11.8 (7.2–16.4)
Lymphadenopathy/hepatosplenomegaly	2	6	4.84 (1.19–19.67)[b]	44.4 (0.0–93.1)

TABLE 2 **Continued**

Characteristic	No. of Children With		Hazard Ratio (95% CI)[a]	Probability of Retinochoroiditis by 4 Years (95% CI), %
	Retinochoroiditis	Congenital Toxoplasmosis		
Postnatal cranial US abnormal	9	24	2.49 (1.01–6.13)[b]	39.4 (19.0–59.8)
Serious neurologic sequelae	4	5	43.31 (10.33–181.55)[b]	80.0 (44.9–100)
Any clinical manifestation				
None (reference)	26	221	1.0	11.8 (7.2–16.4)
Any	15	35	3.65 (1.79–7.46)[b]	46.2 (28.4–64.0)

[a] Data were adjusted for gestational age at maternal seroconversion.

[b] Hazard ratios show an effect that is statistically significant at the 5% level.

[c] European Multicentre Study on Congenital Toxoplasmosis cohort ($n = 256$) is used as data not collected in the Denmark 1992–1996 cohort ($n = 25$).

[d] Data show children in European Multicentre Study on Congenital Toxoplasmosis centers who had no retinochoroiditis on their first postnatal ophthalmoscopy examination before starting postnatal treatment ($n = 218$; ie, 38 excluded, either because of a lesion before 4 months or no examination before 4 months and a first examination with a lesion thereafter). These analyses determine the effect of treatment on lesions that occur for the first time after birth.

[e] Data show mothers in prenatal screening centers ($n = 210$, 3 with missing data on fetal ultrasound result). Five had intracranial lesions on fetal ultrasound 3 ventricular dilatation, and 2 with intracranial calcification. Earliest abnormality was identified at 22.7 weeks of gestation.

1). The shortest interval between a negative examination and a new lesion was 22 days. Twenty children (20 of 281 [7%]) had retinochoroiditis detected at their first ophthalmoscopy: 20 of 50 (40%) children who eventually developed retinochoroiditis had lesions detected at their first postnatal ophthalmoscopy.

Mothers of 103 children received no prenatal treatment, of whom 32 were identified as infected by prenatal screening. Failure to treat these women is probably because they were identified late in pregnancy (median age at first positive test: 38.6 weeks; interquartile range [IQR]: 37.4–40.0 weeks).[5,8] The median age at the start of postnatal treatment was 3 days (IQR: 0–15 days) in prenatal centers and 27 days (IQR: 23–34 days) in European neonatal centers.

Determinants of Age at First Retinochoroidal Lesion

The probability of developing retinochoroiditis by 4 years old was 16% (Table 2). Two prenatal characteristics were statistically significantly associated with the risk of retinochoroiditis (Table 2). Fetal ultrasound abnormalities markedly increased the risk of retinochoroiditis, and all 5 of the children with intracranial abnormalities on fetal ultrasound developed retinochoroiditis. Secondly, there was a weak, but not statistically significant, association between increasing gestational age at maternal seroconversion and a decreased risk of retinochoroiditis. Children whose mothers seroconverted in the first half of pregnancy compared with the second half were twice as likely to develop retinochoroiditis (Fig 1). We found no significant effect of prenatal treatment compared with no treatment or of the timing or type of prenatal treatment on age at first detection of retinochoroiditis (Table 2). This finding is illustrated by the similarity of estimated survivor functions for France, Austria, and Italy and the neonatal screening centers in Scandinavia and Poland (Fig 2). There was no evidence that prenatal treatment significantly reduced the risk of recurrent lesions after birth: the hazard ratio for age at the first or recurrent lesion in children given any treatment compared with none was 1.01 (95% CI: 0.55–1.86).

The timing of prenatal or postnatal treatment, or just of postnatal treatment, was not associated with age at first detection of retinochoroiditis (Table 2). A total of 15 of 50 children (18 of 64 lesion occurrences) had lesions detected while receiving postnatal treatment for between 2 and 64 weeks.

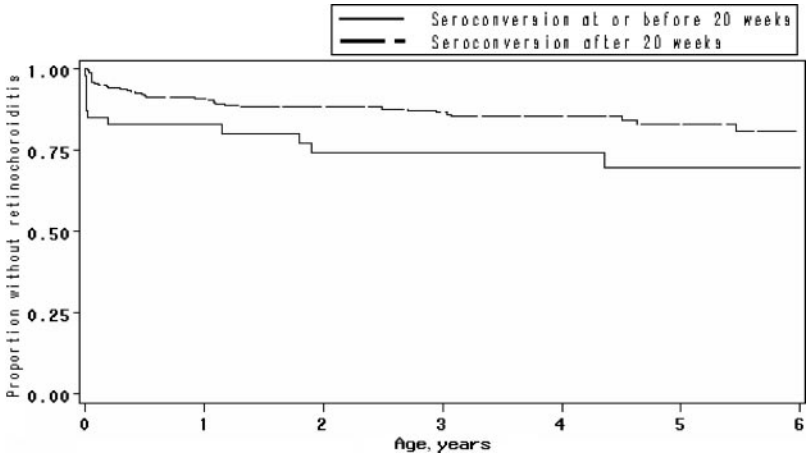

FIGURE 1
Survival analysis showing age at first detection of toxoplasmic retinochoroiditis according to maternal seroconversion before or after 20 weeks' gestation.

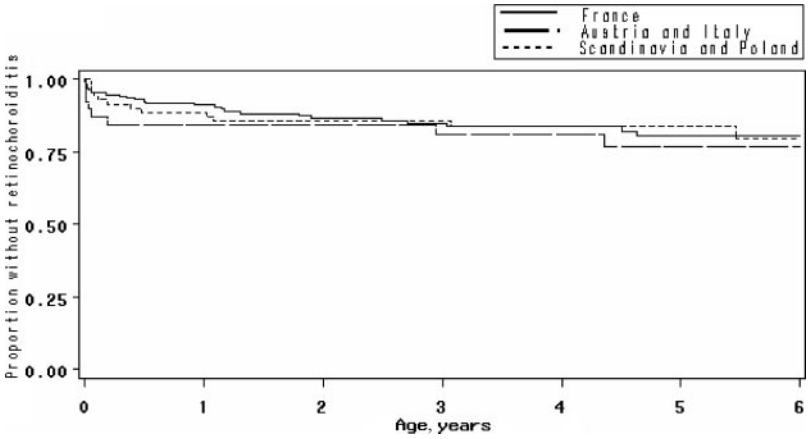

FIGURE 2
Survival analysis age at first detection of toxoplasmic retinochoroiditis according to the region of study and type of screening. Prenatal screening results with monthly retesting in France, every 3 months in Italy or Austria, and neonatal screening in Poland and Scandinavia.

Clinical Manifestations

Children with nonocular manifestations of congenital toxoplasmosis detected before 4 months of age more than doubled their risk of having retinochoroiditis detected at birth or later in childhood compared with children with no manifestations (Table 2). The risk of a first lesion by 4 years of age was highest for children with serious neurologic sequelae (80%) but was also significantly increased for children with intracranial lesions but no serious neurologic impairment (39%) and for those just with lymphadenopathy or hepatosplenomegaly (44%) compared with children with no clinical manifestations (12%; Table 2).

Initial ophthalmoscopy findings, results of intracranial imaging, and the clinical examination would be available to clinicians when they counsel parents about their child's prognosis in early infancy (defined as before 4 months of age). Nearly half of the children who eventually developed retinochoroiditis had already had their first lesion detected before 4 months of age (22 of 50 [44%]), as had 80% of the children with clinical manifestations (12 of 15). Children without retinochoroiditis detected by 4 months had a low risk of developing retinochoroiditis by 4 years (Table 3 and Fig 3), which was similar for children with and without other clinical manifestations (hazard ratio for clinical manifestations in children with no manifestations, group 1, versus those with nonocular manifestations only: 0.92; 95% CI: 0.18–4.56). The risk of recurrent retinochoroiditis in children with lesions detected before 4 months (groups 3 and 4; Table 3 and Fig 3) was high, but because of the small number of events, the CIs were wide.

Results for the effect of prognostic markers on the age at first and recurrent lesions were similar to those for the age at first lesion only (Table 2), but CIs were wider. None of the hazard ratios changed appreciably in sensitivity analyses restricted to French centers or to infants who had a first negative examination after birth or if time 0 was taken as the gestational age at seroconversion rather than birth (results not shown).

DISCUSSION

We found no evidence that prenatal treatment significantly reduced the risk of retinochoroiditis in children with congenital toxoplasmosis followed up to 4 years of age. The main determinants of retinochoroiditis were an abnormal fetal ultrasound showing intracranial abnormalities and the presence of intracranial or systemic clinical manifestations of congenital toxoplasmosis in early infancy. Children with no retinochoroidal lesions detected in early infancy had a low risk of subsequent ocular disease, regardless of the presence of other clinical manifestations. The gestational age at maternal seroconversion had a weak effect on the risk of retinochoroiditis by 4 years.

Our results are based on the largest multicenter study of children with congenital toxoplasmosis and are supported by results from an earlier single-center cohort of 327 infected children in Lyon, France, with a median follow-up of 6 years (79 children had retinochoroidi-

TABLE 3 **Risk of Retinochoroiditis According to Clinical Manifestations Detected Before 4 Months Postnatal Age**

Prognostic Group	Manifestations Before 4 mo		No. of Children With Newly Detected Retinochoroiditis Between 4 mo and 4 y	No. (%) of Infected Children in Prognostic Group (n = 249)[a]	Probability of Retinochoroiditis Between 4 mo and 4 y (95% CI)[b]
	Retinochoroiditis	Other Clinical Manifestations			
1. No manifestations	No	No	17	208 (83.5)	8.0 (4.0–12.1)
2. No retinochoroiditis	No	Yes	3	22 (8.8)	17.9 (0.0–36.5)
3. Retinochoroiditis	Yes	No	3	8 (3.2)	30.0 (0.0–65.7)
4. Both	Yes	Yes	8	11 (4.4)	69.7 (31.1–98.3)

[a] The denominator excludes 25 children in the Danish cohort 1992–1996 and 7 children without follow-up beyond 4 months of age (ie, 281 − 32 = 249).
[b] Data were estimated from survival analyses.

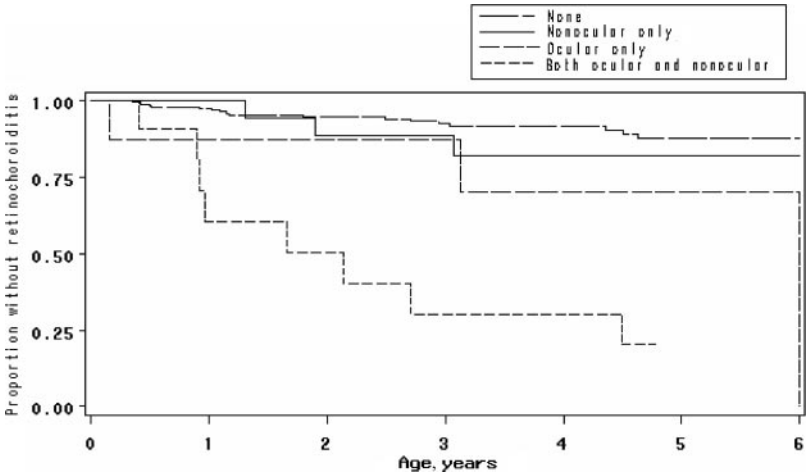

FIGURE 3
Survival analysis showing age at detection of toxoplasmic retinochoroiditis occurring at or after 4 months of age according to the presence of eye and clinical manifestations before 4 months of age.

tis).[2,6] In the Lyon cohort, the risk of retinochoroiditis by 4 years (18%) was very close to our result (16%), and similarly weak, nonsignificant associations were found for gestational age at maternal seroconversion and prenatal treatment.[6] Our study maximized the power to detect an effect of prenatal treatment by virtue of its sample size, length of follow-up, and the large proportion of untreated mothers. Longer follow-up would increase the power to detect a treatment effect but may selectively favor children with retinochoroiditis, who are more likely to comply with follow-up, thereby overestimating the risk of disease.

Findings from previous cohort studies are consistent with our results showing no statistically significant effect of prenatal treatment on retinochoroiditis, even when treatment is given soon after maternal seroconversion.[1,5,12] These findings challenge the rationale for prenatal screening to offer prenatal treatment to prevent ocular disease.

The effect of postnatal treatment has not been addressed by any concurrent comparative studies.[13] In the present study, we examined the effect of delayed starting of postnatal treatment and found no evidence of harm, although the power to detect an effect was limited, because there was little variation in the age at the start of postnatal treatment. We hypothesize that any effect of postnatal treatment is likely to be less than for prenatal treatment, because treatment is likely to be most effective when given soon after maternal seroconversion, before the parasite forms bradyzoite cysts that are impenetrable to antibiotics. Evidence is also lacking about whether postnatal treatment has any effect on recurrent lesions, except for patients with frequent recurrences in Brazil where the *Toxoplasma gondii* genotype is associated with more severe disease.[14] Doubts about the benefits of postnatal treatment are exemplified by varying practice. In a Dutch cohort study, pediatricians could not be persuaded to treat infected infants at all,[13] and in the Danish National Screening Program, treatment was given for just 3 months. The Danish screening program, which started in 1992, was stopped in August 2007 because of the low burden of disease and a lack of evidence that treatment is effective (E. Petersen, written communication, 2007).[5] The long-standing practice of treating for 1 year, or in some centers, 2 years after birth[1] has no defensible evidence base and presents a considerable burden for the child and family, as well as risk of adverse effects requiring stopping treatment ranging from 14% to 58%.[15]

Evidence is needed of the effectiveness of repeated routine ophthalmic examinations throughout childhood for children with normal ophthalmoscopy in early infancy who have a low risk of retinochoroiditis. Instead, clinicians could advise parents to bring the child for assessment should ocular signs or symptoms develop and ensure that routine school vision screening is undertaken at 3 to 4 years old. In the Danish study, ophthalmologists could not be persuaded of the benefits of annual ophthalmoscopy examinations (E. Petersen, verbal communication, 2004), whereas in some centers examinations are repeated at 6 monthly intervals. We reported previously that at 3 to 4 years, infected and uninfected children born to toxoplasma-infected mothers had no detectable differences in a range of developmental outcomes, but parents of infected children were significantly more anxious.[16] Part of this anxiety may be attributable to concerns about vision loss in their child, a fear that is reinforced by repeated examinations.

Implications for Follow-up

Currently, all children with congenital toxoplasmosis identified by prenatal or neonatal screening are treated postnatally and followed up throughout childhood. Our results provide an evidence base for an alternative strategy in which postnatal treatment and routine follow-up is offered according to prognosis, taking into account the lack of evidence for a significant effect of postnatal treatment (Table 3). We suggest that 91% (20 of 230) of infected children who are at lower risk of retinochoroiditis (groups 1 and 2) could be offered a short course or no postnatal treatment. Instead of routine annual ophthalmic examinations, parents could request an assessment if the child develops ocular symptoms or signs. Routine ophthalmic follow-up is likely to be most important for children with early clinical manifestations and/or retinochoroiditis (groups 3 and 4), who have a high risk of

recurrent lesions and compose 5% (12 of 256) of all infected infants. Although generalizable to regions in which *T gondii* type 2 strain predominates (Europe and North America), these findings may not apply to areas with more virulent strains, most notably central and South America.[17,18]

CONCLUSION

In this European cohort we found no evidence that prenatal treatment statistically significantly reduced the risk of retinochoroiditis. Although the analysis of postnatal treatment lacked power, it seems unlikely that postnatal treatment would be more effective than prenatal treatment for retinochoroiditis. Given these findings and the low risk of retinochoroiditis in ~90% of children with congenital toxoplasmosis, clinicians need to reconsider their practice of repeated ophthalmoscopy throughout childhood combined with postnatal treatment during infancy. An alternative approach might be to confine treatment and follow-up to the minority of children with early clinical manifestations and ocular disease who are most at risk of new ocular lesions postnatally. For the remainder, the effectiveness of postnatal treatment and follow-up should be evaluated in a randomized, controlled clinical trial.

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REFERENCES

1. Gras L, Wallon M, Pollak A, et al. Association between prenatal treatment and clinical manifestations of congenital toxoplasmosis in infancy: a cohort study in 13 European centers. *Acta Paediatr.* 2005;94(12):1–12
2. Wallon M, Kodjikian L, Binquet C, et al. Long-term ocular prognosis in 327 children with congenital toxoplasmosis. *Pediatrics.* 2004;113(6):1567–1572
3. Tan HK, Schmidt D, Stanford MR, et al. Risk of visual impairment in children with congenital toxoplasmic retinochoroiditis. *Am J Ophthalmol.* 2007;144(5):648–653
4. Gilbert R, Dezateux C. Newborn screening for congenital toxoplasmosis: feasible, but benefits are not established. *Arch Dis Child.* 2006;91(8):629–631
5. SYROCOT (Systematic Review on Congenital Toxoplasmosis) study group, Thiébaut R, Leproust S, Chêne G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet.* 2007;369(9556):115–122
6. Binquet C, Wallon M, Quantin C, et al. Prognostic factors for the long-term development of ocular lesions in 327 children with congenital toxoplasmosis. *Epidemiol Infect.* 2003;131(3):1157–1168
7. Lebech M, Andersen O, Christensen NC, et al. Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. *Lancet.* 1999;353(9167):1834–1837
8. Gilbert R, Gras L. Effect of timing and type of treatment on the risk of mother to child transmission of Toxoplasma gondii. *BJOG.* 2003;110(2):112–120
9. Thalib L, Gras L, Romand S, et al. Prediction of congenital toxoplasmosis by polymerase chain reaction analysis of amniotic fluid. *BJOG.* 2005;112(5):567–574
10. Therneau TM, Grambsch PM. *Multiple Events Per Subject. Modeling Survival Data: Extending the Cox Model.* New York, NY: Springer-Verlag; 2000:169–194
11. Thulliez P. Screening programme for congenital toxoplasmosis in France. *Scand J Infect Dis.* 1992;84(suppl):43–45
12. 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(6):1309–1330
13. Gilbert R, Dunn D, Wallon M, et al. Ecological comparison of the risks of mother-to-child transmission and clinical manifestations of congenital toxoplasmosis according to prenatal treatment protocol. *Epidemiol Infect.* 2001;127(1):113–120
14. Gilbert RE, Harden M, Stanford MR. Antibiotics versus control for toxoplasma retinochoroiditis. *Cochrane Database Syst Rev.* 2002;(1)
15. Daveluy A, Haramburu F, Bricout H, et al. *Review of Data Related to Side Effects of Drugs Used in Congenital Toxoplasmosis*. Bordeaux, France: EUROTOXO A European Consensus on the State of the Science; 2005
16. Freeman K, Salt A, Prusa A, et al. Association between congenital toxoplasmosis and parent-reported developmental outcomes, concerns and impairments, in 3 year old children. *BMC Pediatr.* 2005;5:23
17. Lehmann T, Marcet PL, Graham DH, Dahl ER, Dubey JP. Globalization and the population structure of Toxoplasma gondii. *Proc Natl Acad Sci U S A.* 2006;103(30):11423–11428
18. Ajzenberg D, Banuls AL, Su C, et al. Genetic diversity, clonality and sexuality in Toxoplasma gondii. *Int J Parasitol.* 2004;34(10):1185–1196

Predictors of Retinochoroiditis in Children With Congenital Toxoplasmosis: European, Prospective Cohort Study

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