Association between congenital toxoplasmosis and preterm birth, low birthweight and small for gestational age birth

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Objective To determine the association between congenital toxoplasmosis and preterm birth, low birthweight and small for gestational age birth.

Design Multicentre prospective cohort study.

Setting Ten European centres offering prenatal screening for toxoplasmosis.

Population Deliveries after 23 weeks of gestation in 386 women with singleton pregnancies who seroconverted to toxoplasma infection before 20 weeks of gestation. Deliveries after 36 weeks in 234 women who seroconverted at 20 weeks or later, and tested positive before 37 weeks.

Methods Comparison of infected and uninfected births, adjusted for parity and country of birth.

Main outcome measures Differences in gestational age at birth, birthweight and birthweight centile.

Results Infected babies were born or delivered earlier than uninfected babies: the mean difference for seroconverters before 20 weeks was −5.4 days (95% CI: −1.4, −9.4), and at 20 weeks or more, −2.6 days (95% CI: −0.5, −4.7). Congenital infection was associated with an increased risk of preterm delivery when seroconversion occurred before 20 weeks (OR 4.71; 95% CI: 2.03, 10.9). No significant differences were detected for birthweight or birthweight centile.

Conclusion Babies with congenital toxoplasmosis were born earlier than uninfected babies but the mechanism leading to shorter length of gestation is unknown. Congenital infection could precipitate early delivery or prompt caesarean section or induction of delivery. We found no evidence for a significant association between congenital toxoplasmosis and reduced birthweight or small for gestational age birth.

INTRODUCTION

Congenital toxoplasmosis is caused by transplacental transmission of the parasite *Toxoplasma gondii* in women that acquire the infection during pregnancy. As few women have symptoms, maternal infection is detected by testing for seroconversion of toxoplasma specific antibodies. The risk of transmission increases steeply with gestational age at maternal seroconversion. Congenital toxoplasmosis is associated with signs of intracranial calcification, hydrocephalus and/or retinochoroiditis in approximately one in six infants, and with perinatal death or severe disseminated infection in 1–2% of cases. Reported rates of congenital toxoplasmosis range from less than 1 per 10,000 live births in Massachusetts, Austria, Sweden and Norway; 2–3 per 10,000 live births in Poland and Brazil; and 1 per 1000 in France.

Congenital toxoplasmosis has long been considered a cause of intrauterine growth retardation. Serological testing for congenital toxoplasmosis is still recommended as one component of the TORCH screen (acronym for toxoplasmosis, other infections, rubella, cytomegalovirus...
and herpes simplex virus) for unexplained intrauterine growth retardation. However, evidence for an association between growth retardation and congenital toxoplasmosis is limited to reports of case series referred for clinical problems. To date, no population-based studies have investigated the effect of congenital toxoplasmosis on size or weeks of gestation at birth.

In this report, we analysed a large prospective cohort of women who seroconverted to toxoplasma infection during pregnancy to determine whether congenital toxoplasmosis is associated with preterm delivery, low birthweight or being small for gestational age.

METHODS

The study was based on women enrolled in the European Multicentre Study on Congenital Toxoplasmosis (EMS-COT) for which methods have been reported in detail elsewhere. Women were identified by serological testing which was repeated in susceptible women each month in France, and three monthly elsewhere. The analysis was restricted to women who seroconverted during pregnancy and had a singleton birth. Women who had a spontaneous miscarriage or termination of pregnancy before 24 weeks of gestation were excluded as they were not routinely investigated for maternal and congenital toxoplasmosis, and birthweight was not always recorded. We also excluded mother–child pairs identified by neonatal screening for congenital toxoplasmosis because perinatal deaths and preterm deliveries would be under-represented. Stillbirths were excluded from the analyses because the date of death was unknown and may have occurred several days before delivery. Inclusion of stillbirths could therefore introduce bias in favour of lower birthweight centile. Terminations of pregnancy were excluded from analyses of gestational age at delivery and birthweight as these outcomes were determined by the timing of termination. We also excluded terminations from analyses of birthweight centile standardised for gestational age and sex as information was lacking on the baby’s sex (Fig. 1). Congenital infection status was measured as previously defined. The study complied with the research ethics requirements in each participating country.

We hypothesised that fetal toxoplasma infection could cause premature onset of labour due to inflammatory mediators, and it could inhibit fetal growth. The primary outcomes were therefore gestational age at birth, and the gestational age- and sex-standardised birthweight centile reflecting babies born small for gestational age. We used the clinician’s best estimate of the expected date of birth based on an early prenatal dating ultrasound scan, if available, and date of last menstrual period. Standardised scores (z-scores) were calculated for birthweight using sex- and gestational-age-specific growth reference standards. Secondary outcomes were birthweight, and each of the outcomes dichotomised.

Prenatal treatment was analysed as the interval between seroconversion and the start of any type of treatment or, if untreated, delivery (treatment delay). We also analysed the type of initial treatment (spiramycin, pyrimethamine–sulphonamide or no treatment). Treatment regimens have been described in detail elsewhere. Subsequent treatment changes, for example, from spiramycin to pyrimethamine–sulphonamide, could not be considered, as they were conditional on the results of prenatal diagnosis for congenital infection status.

Maternal seroconversion was estimated to occur at the midpoint between the last negative IgM test and the first positive IgM test unless no IgG was found when IgM was first positive, in which case the date of seroconversion was considered to be 14 days before the date of the first positive IgM test. Women identified by tests for recent infection (for example, with specific IgG and IgM positive tests and low IgG avidity at the first prenatal test) who gave birth to an infected child were assumed to have their last negative IgM test at conception. Other covariates were country (France vs Italy or Austria), maternal age and parity. Other factors associated with low birthweight and preterm delivery, such as socio-economic status and maternal smoking, were not recorded for the study. These factors would confound the analyses only if they are associated with mother-to-child transmission. We know of no experimental or observational data to indicate whether this is the case or not. No information was collected on the mode of delivery.

Analyses were constructed to avoid the inherent correlation between gestational age at seroconversion and gestation at birth. For example, pregnant women that seroconvert at 38 weeks of gestation are not at risk of preterm delivery as seroconversion must necessarily precede birth. We made an a priori decision to separately analyse seroconverters from the first (less than 20 weeks) and second halves of pregnancy as the effect of congenital toxoplasmosis on outcome is likely to be greater the earlier fetal infection occurs. Multiple regression models were derived for the three continuous outcomes to determine the significance of differences between infected and uninfected births accounting for covariates. Logistic regression models were derived for these outcomes dichotomised as follows: preterm delivery (<37 weeks of gestation), low birthweight (<2500 g) and small for gestational age birth (<10th centile for age and sex standardised birthweight). Resulting odds ratios represent the risk of an unfavourable outcome given an infected versus uninfected fetus. A backward stepwise approach was used for all multivariate analyses. Country and parity were kept in all models because of established differences in population norms among countries and the association between parity and birthweight. Other potential confounders included in initial models were gestation at seroconversion and its interaction with congenital infection status, maternal age and its square, treatment delay and its interaction with congenital infection status, and type of first treatment. Variance inflation factors were
computed for each variable, and potentially confounding variables and variance inflation factor values exceeding 10 were excluded from further model development. Variables were retained in the final model if significant at $P < 0.05$. Main effects were included if interactions were significant.

The second analysis involved women who seroconverted at or after 20 weeks of gestation. We limited the analysis to women who had their first positive IgM test before 37 weeks and delivered at 37 or more weeks of gestation in order to ensure that all women were at risk of the outcome. The statistical approach was the same as that used above except that for logistic regression, gestation at birth was dichotomised near the median (<40 weeks). Statistical analyses were performed using SAS version 8.2.

RESULTS

Figure 1 shows the number of women included in the analyses. Tables 1 and 2 show the prevalence of preterm delivery, low birthweight and small for gestational age birth according to congenital infection status, as well as results of univariate and multivariate analyses.

**Seroconversion before 20 weeks of gestation**

Of the 386 women who seroconverted before 20 weeks, 42 (11%) gave birth to infected babies (Table 1). Five women had terminations at 24 weeks or more. All five were performed for toxoplasmosis and all the fetuses were infected (weeks of gestation at termination were 24, 27, 27, 28, 33). There were three stillbirths and all were uninfected (weeks of gestation at delivery were 31, 33 and 40). The mean maternal age was 27.6 years (SD 4.8) and almost half ($n = 163, 45\%$) had no other children. The majority of women ($n = 278, 72\%$) were enrolled from French centres. The median gestation at seroconversion was 13.8 weeks (range: 1.5, to 19.9) and almost all ($n = 383, 99\%$) were treated, mostly with spiramycin as the first treatment ($n = 315, 82\%$). The median interval between seroconversion and the start of treatment was 31 days (range: 7, to 262 days).

Infants with congenital toxoplasmosis had a reduced length of gestation relative to uninfected infants (mean reduction 5.4 days; 95% CI: 1.4, 9.4), and were significantly more likely to be born before 37 weeks (Fig. 2A). Preterm birth occurred in 11/42 (25%) infected babies (the earliest at 34.6 weeks), compared with 31/342 (9.1%, earliest at 30.4 weeks; 10 were born before 34 weeks).

**Fig. 1.** Flow diagram to show patients included in the analyses.
Country of birth was significantly associated with a shorter length of gestation for babies born in France versus elsewhere (mean difference 4.6 days; \(P = 0.001\)). The length of gestation did not differ significantly in women with a positive versus negative prenatal diagnosis (mean difference /C0 4.5 days; 95% CI: /C0 10.1, 1.2), or in women with infected versus uninfected fetuses who had no prenatal diagnosis (mean difference /C0 2.7 days; 95% CI: /C0 9.2, 3.7).

There was no significant association between congenital toxoplasmosis and birthweight or being small for gestational age. Parity was a significant confounding factor for birthweight (\(P = 0.01\)) and parity and country were significant confounders for smallness for gestational age (\(P = 0.04\) and \(P = 0.01\), respectively).

There was no significant interaction between gestational age at seroconversion and congenital infection status for any of the outcomes.

### Seroconversion at 20 weeks of gestation or later

A total of 234 women seroconverted at 20 weeks or later, had their first positive IgM test before 37 weeks and gave birth after 36 weeks of gestation. Of these, 104 (44.4%) had

### Table 1. Mean differences and odds ratios for gestation at birth, birthweight and birthweight centile according to congenital infection status in women who seroconverted before 20 weeks of gestation.

<table>
<thead>
<tr>
<th>Distribution of births (n)</th>
<th>Mean difference</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR(^{1}) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestation at birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
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</tr>
<tr>
<td>CT</td>
<td>11</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>31</td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>≥37 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>31</td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>62</td>
<td>342</td>
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</tr>
<tr>
<td><strong>Birthweight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>6</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
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<td>315</td>
<td></td>
</tr>
<tr>
<td>Total</td>
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<td>350</td>
<td></td>
</tr>
<tr>
<td>≥2500 g</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CT</td>
<td>25</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>106</td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>346</td>
<td></td>
</tr>
<tr>
<td><strong>Birthweight centile(^{1})</strong></td>
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<tr>
<td>&lt;10th centile</td>
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</tr>
<tr>
<td>CT</td>
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<td></td>
</tr>
<tr>
<td>No CT</td>
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<td>306</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>≥10th centile</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CT</td>
<td>20</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>106</td>
<td>311</td>
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</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>346</td>
<td></td>
</tr>
</tbody>
</table>

CT = congenital toxoplasmosis.

\(^{1}\) Standardised for gestational age and sex.

\(^{2}\) Adjusted for country and parity.

### Table 2. Mean differences and odds ratios for gestation at birth after 37 weeks, birthweight and birthweight centile according to congenital infection status in women who seroconverted at 20 weeks or more of gestation.

<table>
<thead>
<tr>
<th>Distribution of births (n)</th>
<th>Mean difference</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR(^{1}) (95% CI)</th>
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</thead>
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<tr>
<td><strong>Gestation at birth</strong></td>
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<td>CT</td>
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<td></td>
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<tr>
<td>No CT</td>
<td>77</td>
<td>52</td>
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<tr>
<td>Overall</td>
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<tr>
<td>≥40 weeks</td>
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<tr>
<td>CT</td>
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<tr>
<td>No CT</td>
<td>52</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>106</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td><strong>Birthweight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CT</td>
<td>3</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>3</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
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<td>227</td>
<td></td>
</tr>
<tr>
<td>≥2500 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>106</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
<td>126</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>232</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td><strong>Birthweight centile(^{1})</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;10th centile</td>
<td></td>
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<tr>
<td>CT</td>
<td>8</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>No CT</td>
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<td>117</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
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<td>212</td>
<td></td>
</tr>
<tr>
<td>≥10th centile</td>
<td></td>
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</tr>
<tr>
<td>CT</td>
<td>95</td>
<td>95</td>
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<tr>
<td>No CT</td>
<td>117</td>
<td>117</td>
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</tr>
<tr>
<td>Overall</td>
<td>212</td>
<td>212</td>
<td></td>
</tr>
</tbody>
</table>

CT = congenital toxoplasmosis.

\(^{1}\) Standardised for gestational age and sex.

\(^{2}\) Adjusted for country and parity.
infected babies, one had a stillbirth and none had a ter-
mination. The average maternal age was 29.2 years (SD 4.9),
and the majority (n = 193, 82.5%) were enrolled from
French centres. Almost all women were treated (n = 225,
96.2%), with spiramycin as the first treatment in 181 cases
(77.4%). The median gestation at seroconversion was 27.2
weeks (range: 20–35 weeks) and the median treatment
delay was 24.3 days (21, 143 days).

Congenital toxoplasmosis significantly reduced gestation-
al age at birth (mean difference \(-2.6\) days; 95% CI: \(-4.7,
-0.5\)) (Fig. 2B). Babies in France were born significantly
earlier (mean \(-6.4\) days; \(P < 0.0001\)).

There was no significant association between congenital
toxoplasmosis and mean birthweight or with low birth-
weight. However, confidence intervals for these analyses
were wide due to the small number of infants with low
birthweight. Parity was a significant confounder when
birthweight was analysed as a continuous variable (\(P =
0.02\)). There was no significant association between con-
genital toxoplasmosis and standardised birthweight. Coun-
try of birth and parity were significant confounding factors
(\(P < 0.01\)).

DISCUSSION

Congenital toxoplasmosis was associated with reduced
length of gestation in women seroconverting before and
after 20 weeks. We found no significant association be-
tween congenital toxoplasmosis and birthweight or small
for gestational age birth.

Strengths of the study include the fact the women were
identified prospectively by prenatal screening for maternal
infection, and enrolled before any attempt was made to
diagnose fetal infection. This reduced the potential for se-
lection bias due to investigation of congenital infection in
small for gestational age or preterm births. A limitation is
that information was not available on whether labour was
spontaneous or induced, or whether delivery was by cae-
sarean section. In addition, we found no clear evidence that
length of gestation was shorter in women with a positive
versus negative prenatal diagnosis. Consequently, it is not
possible to determine whether the association between con-
genital toxoplasmosis and length of gestation is due to in-
duction of labour or caesarean section or due to spontaneous
onset of labour. Obstetric intervention may partly explain
the finding of earlier gestational age at delivery in the
French centres. In addition, although we used the most ac-
curate estimate available for the expected date of delivery,
methods for computing this date may have varied among
countries.

A further limitation was that we could not investigate the
effects of treatment versus no treatment as there were few
untreated women. However, we found no significant effect
of the timing or type of treatment on any of the outcomes.
Well-known risk factors for preterm delivery or small for
gestational age birth, such as maternal smoking, socio-
economic status and ethnicity, were not measured in this
study. At the time the study was initiated, we knew of no
association between these factors and mother-to-child
transmission of toxoplasmosis; no evidence has emerged
since.

As there was no comparison group of uninfected women,
we were not able to determine whether there was any in-
dependent effect of maternal infection on gestation or small
for gestational age birth. However, a recent large cohort
study found no evidence of an association between fever in
early pregnancy and fetal death.\(^{18}\)

We did not analyse the effect of congenital toxoplasmo-
sis on spontaneous miscarriage or stillbirth. This was
because of the small number of fetal losses, the possibility
of selection bias favouring infected fetuses and the fact that
fetal losses were often not investigated for congenital toxo-
plasmosis. Instead, we compared total fetal losses using a
subset of pregnant women (10/448) from the EMSCOT
study with a first positive IgM test in the first trimester,
standardising for maternal age using the age distribution re-
ported in a study of unselected women with viable preg-
nancies at 10 weeks of gestation.\(^{19}\) The rate of spontaneous
fetal loss before 28 weeks among toxoplasma-infected

\(^{18}\) Arch Dis Child Fetal Neonatal Ed 2004;89:F134–F138

\(^{19}\) Br J Obstet Gynaecol 2005;112:1326–1331
women in the EMSCOT cohort was 2.48% (95% CI: 0.04, 4.03), similar to the rate reported by Gilmore and McNay of 2.1% (1.50, 2.84). Out of 10 fetal losses in this subset of the EMSCOT cohort, two had congenital infection based on a positive prenatal diagnosis (PCR positive) and autopsy, two had a negative prenatal diagnosis (PCR negative) and six were not investigated.

The study is the first population-based study of the effect of congenital infection on gestation and smallness at birth. Sever et al. previously reported an association between low birthweight and high titres (>1024) for toxoplasma-specific IgG in women post-delivery (relative risk 1.4; P < 0.01). However, congenital infection status was not measured nor was there any exploration of confounding due to factors that affect maternal exposure to infection.

For babies with congenital infection, the clinical consequences of being born on average 5.4 days earlier are unlikely to be serious unless delivery takes place before 30 weeks of gestation. Although 25% (95% CI: 12.5, 39.9) of infected babies were born preterm, compared with 9% (95% CI: 6.1, 12.1) of uninfected babies, none of the infected babies were born before 34 weeks. However, further studies are required that include information on the onset of labour and mode of delivery to determine whether shorter length of gestation is related to obstetric intervention or a consequence of fetal infection.

CONCLUSION

Congenital toxoplasmosis was associated with shorter length of gestation at birth but the mechanisms underlying this association require further exploration. We found no evidence to support the view that congenital toxoplasmosis retards fetal growth. Nevertheless, given that there were only 146 infected infants in the study, we cannot exclude a possible effect of T. gondii on fetal growth in individual cases.

Acknowledgements

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Study design and co-ordination


Statistical analysis


References

11. Kliegman RM, Updala GD. Intrauterine growth retardation. In:

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