The Austrian Toxoplasmosis Register, 1992–2008

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Background. We aimed to determine the incidence of primary gestational infections with Toxoplasma gondii and congenital toxoplasmosis in Austria, a country with a nationwide prenatal serological screening program since 1974.

Methods. We analyzed retrospective data from the Austrian Toxoplasmosis Register of pregnant women with Toxoplasma infection and their offspring with births between 1992 and 2008, identified by the prenatal mandatory screening program. Treatment was administered to women from diagnosis of a Toxoplasma infection until delivery. Infected infants were treated up to 1 year of life routinely. Clinical manifestations in infected infants were monitored at least for 1 year and documented in the register.

Results. The Austrian Toxoplasmosis Register included 2147 pregnant women with suspected Toxoplasma infection. Annually, 8.5 per 10 000 women acquired Toxoplasma infection during pregnancy, and 1.0 per 10 000 infants had congenital toxoplasmosis (13% mean transmission rate). Our data showed that women treated according to the Austrian scheme had a 6-fold decrease in the maternofetal transmission rate compared to women without treatment.

Conclusions. Results from the Austrian Toxoplasmosis Register show the efficiency of the prenatal screening program. Our results are of clinical relevance for infants, healthcare systems, and policy makers to consider preventive Toxoplasma screening as a potential tool to reduce the incidence of congenital toxoplasmosis.

Keywords. congenital toxoplasmosis; Toxoplasma gondii; incidence; register; database.

Primary gestational infection (PGI) with Toxoplasma gondii and congenital toxoplasmosis is a worldwide health problem, and the best strategy to prevent this disease has not been determined [1]. Clinical manifestations of congenital disease include retinochoroiditis, cerebral calcifications, hydrocephalus, mental retardation, and death [2–5]. Efficacy of screening and treatment programs in an attempt to reduce vertical transmission of the parasite and clinical manifestations of congenital toxoplasmosis have been the subject of controversy and worldwide debate despite several studies that have shown the benefit of these programs [6–20]. Hence, there is a great need to report the incidence of PGI as well as the efficacy of treatment protocols during gestation to prevent and treat congenital toxoplasmosis.

Infected infants are often clinically asymptomatic at birth, and thus their infection might remain unrecognized, leading to risk of severe sequelae [14, 16]. In adults, the infection usually remains asymptomatic and unnoticed [1]. Only systematic serologic testing in pregnant women and infants can accurately reveal whether PGI has occurred in the mother and, if so, transmitted to the infant [21, 22]. The frequency and severity of congenital toxoplasmosis depend on several factors including maternal onset of infection, treatment, strain, women’s immune response, and placental permeability [23].

Different surveillance programs have been established to monitor PGI [24]. In Austria, Toxoplasma screening of pregnant women is part of the “mother-child-booklet” (www.help.gv.at) and covered by national healthcare providers and Ministry of Health [25]. Prenatal care is mandatory to receive parental leave allowance [21]. First-line serologic screening is scheduled within the first trimester, and analyses are performed by
clinical laboratories. In Austria, 30%–40% of women show infection prior to pregnancy, and no further tests are required [26, 27]. In contrast, it is important to retest seronegative women bimonthly. In case of PGI, treatment is administrated until birth. Since 1992, amniocentesis and Toxoplasma-specific polymerase chain reaction (PCR) have been used for diagnosis in affected women and to determine treatment management [28, 29]. In situations of congenital toxoplasmosis, treatment of the infant is prescribed during the first year of life.

In this study, we analyzed both obstetric and pediatric data collected in the unique Austrian Toxoplasmosis Register with respect to reported incidences of PGI and transmission to the fetus, as well as standardized follow-up data of infants with congenital toxoplasmosis (birth cohort 1992–2008) in Austria. We report the clinical outcome of 2147 pregnant women and 141 infants with congenital toxoplasmosis up to the end of the first year of life of the infant. Data analysis includes serology, treatment, and clinical follow-up.

**METHODS**

The Austrian Toxoplasmosis Register was established at the Reference Laboratory, Medical University of Vienna. In this study, all immunocompetent pregnant women with suspicion of PGI identified by the mandatory serological screening and their offspring were included. Women with known immunodeficiency or metabolic diseases were excluded from analysis. In this study, we analyzed data from the birth cohort 1992–2008. This register collected nationwide data on serology of both mother and infant, prenatal ultrasound, treatment, and amniocentesis as well as clinical follow-up data of the infant. The medical care of women and infants was provided by local physicians. In addition, the Reference Laboratory offered counseling by medical experts for local physicians and families on prevention strategies such as hygienic measures and nutrition, diagnosing toxoplasmosis, testing, treatment, prenatal diagnostics, risk to the fetus resulting in congenital toxoplasmosis, and clinical examinations. The interdisciplinary cooperation of clinical laboratories, prenatal care centers, physicians, midwives, and parents contributed to this register. A nationwide survey evaluated the register sufficiency 3 times over a 2-year period (unpublished data) to consider that all identified infections were recorded. This survey included pregnant women and infants, and collected data on both PGI and congenital toxoplasmosis by interviews or questionnaires sent to clinical laboratories, prenatal care centers, and healthcare facilities.

Records on the routine visits of the infant’s care by local physician(s) included clinical data at birth, during the neonatal period, 4 times during the first year of life, and then once a year until the age of 5 years. The medical care routinely comprised hearing assessment and physical and neurodevelopmental examinations. Infants enrolled in this register had additional examinations, such as serology (at birth, then every 3 months during the first year of life), cranial ultrasound, and funduscopically according to a standardized program.

**Classification**

The maternal infectious status was assigned retrospectively by the Reference Laboratory using criteria determined by the European Research Network on congenital toxoplasmosis [30]. Women with seroconversions and potential infections were classified as having PGI. Infants were classified as follows: (1) congenital toxoplasmosis, determined by the persistence of anti-Toxoplasma immunoglobulin G (IgG) antibodies beyond the age of 1 year, positive PCR from amniotic fluid, or histopathological isolation of parasite; or (2) noninfected infants, with maternally transmitted antibodies, identified by negative Toxoplasma-specific IgG during the first year of life.

Serum samples were analyzed routinely by different automated test systems in clinical laboratories. In general, all institutions were certified for quality management according to the International Organization for Standardization from Quality Austria. All of these laboratories had contracts with the health insurance plans to get reimbursements for the analyses. In case of undetermined infection status, the in-house Sabin-Feldman dye test and immunoglobulin M immunosorbent agglutination assay (bioMérieux) were performed at the Reference Laboratory. The PCR analyses of amniotic fluid samples were only performed with the same protocol at the Medical University of Vienna [31].

**Treatment**

Category I, Austrian treatment scheme: Pregnant women with PGI were treated continuously after diagnosis until birth [32]. Until 16 weeks of gestational age, spiramycin (2.3 g per day in 3 dosages) was prescribed. Afterward, prescription was dependent on PCR result of amniotic fluid: (a) negative PCR, spiramycin only; (b) no PCR or positive PCR, 4-weeks pyrimethamine (50 mg first dose, then 25 mg daily) in combination with sulfadiazine (1.5 g first dose, then 0.75 g daily) and folinic acid (15 mg 3 times weekly) alternating with 4-weeks spiramycin.

Importantly, in infants with congenital toxoplasmosis or high risk of transmission, treatment was initiated as soon as possible after birth and continued for 12 months [32]. The daily dosage was 100 mg/kg (in 2 doses) spiramycin alternating with combination of 1 mg/kg pyrimethamine, 85 mg/kg (in 4 doses) sulfadiazine, and 5 mg twice-weekly folinic acid. Prescription of therapy depended on whether clinical manifestations of congenital toxoplasmosis were present. In infants with clinical manifestations, the pyrimethamine/sulfadiazine/folic acid regimen was prescribed for the first 6 months of life, followed by the alternating treatment scheme (6 weeks...
Table 1. Impact of Maternal Treatment on Maternofetal Transmission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary Gestational Infection, No. (%)</th>
<th>Congenital Toxoplasmosis, No. (%)</th>
<th>Transmission Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austrian scheme</td>
<td>1007 (85.8)</td>
<td>87 (61.7)</td>
<td>8.6 (6.9–10.4)</td>
</tr>
<tr>
<td>Other regimens</td>
<td>103 (8.8)</td>
<td>22 (15.6)</td>
<td>21.4 (13.4–29.3)</td>
</tr>
<tr>
<td>No treatment</td>
<td>63 (5.4)</td>
<td>32 (22.7)</td>
<td>50.8 (38.5–63.1)</td>
</tr>
<tr>
<td>Total No.</td>
<td>1173</td>
<td>141</td>
<td></td>
</tr>
</tbody>
</table>

A statistical difference was observed for the transmission rate between the Austrian scheme, other regimens, and no treatment in both the univariable logistic regression as well as in the adjusted model (P < .001); for detail, see the Statistical Analysis section.

Abbreviation: CI, confidence interval.

spiramycin and 4-weeks combination) for additional 6 months. In infants without symptoms, combination was prescribed for the first 6 weeks of life, followed by the alternating treatment (6-weeks spiramycin and 4-weeks combination).

Category II, other regimens: The prescription did not comply with national guidelines. Differences exist in length of treatment, dosage, and use of other drugs (clindamycin, josamycin, co-trimoxazole).

Category III, no treatment: Reasons were, for example, delayed diagnosis of infection, lack of prescription, or intake refusal.

Statistical Analysis

Categorical variables were described as absolute and relative frequencies. Transmission rate according to treatment was calculated and displayed with 95% confidence intervals (CIs) (Table 1). Continuous variables were presented as mean and standard deviation (SD) or as median and quartiles if some of the variables in the table showed asymmetric distributions, and compared between trimesters using Kruskal–Wallis tests. Influences of treatment and various other risk factors on transmission were investigated by univariable and multivariable logistic regression models for which crude and adjusted odds ratios (ORs), respectively, were given with 95% CI. For this purpose, treatment delay was classified as <4, 4 to <8, and ≥8 weeks, and nested into respective treatment. Treatment duration also entered the models as nested in treatment variable, whereas interval between seronegativity and seropositivity was nested in an indicator for seroconversion. Indicator for trimester of infection was constructed with maximally possible information content (eg, indicator for first trimester equal to zero if “second or third trimester” was given). All continuous variables were tested for nonlinear influences (although none were significant). Apart from nested effects, the preselected interaction investigated was trimester of infection and therapy delay. From the multivariable model, factors were removed if their effect was not significant and their removal had no relevant influence on effect estimates of remaining variables. Due to interaction of treatment and duration (via nesting), the OR was presented depending on duration. To give an estimate of dependence of transmission on the time of PGI, the multivariable model was repeated, replacing trimester of infection by weeks of gestational age, which was available in fewer cases. Duration of pregnancy was calculated by postmenstrual age. All trimester were divided in first (weeks <13), second (weeks 13–26), and third (weeks 27–43). P values are results of 2-sided tests. All computations have been performed using SAS version 9.2 (SAS Institute Inc).

Ethics Statement

The local ethics committee at the Medical University of Vienna, Austria, approved this study (no. 824/2009). All women and parents of infants included gave their informed consent.

RESULTS

In this 17-year period (1992–2008), 1 387 680 women (including 19 267 multiple births) gave birth (www.statistik.at) and were screened for Toxoplasma-specific antibodies. A total of 2147 women with suspected Toxoplasma infection were reported and documented in the toxoplasmosis register. After retrospective analysis of serology data, a total of 974 (45.4%; 95% CI, 43.2%–47.5%) of these women had infection before actual pregnancy, and none of their offspring were infected. This group was excluded from further statistical analysis.

PGI occurred in the remaining 1173 (54.6%) cases. Less than 3% of these cases were identified with swollen lymph nodes, and 0.2% had contact with cats or the consumption of raw meat. Maternal drug intolerance using the standard treatment was reported in 5 of 1007 (0.5%; 95% CI, .16%–1.15%) cases including rash, anemia, or vomiting, but all symptoms disappeared spontaneously. In only 1 of these cases, an allergic reaction with shortness of breath and swollen tongue after the intake of sulfadiazine and pyrimethamine was reported. These symptoms rapidly disappeared after termination of intake and no further medical intervention was necessary. In 707 of 1173 (60.3%; 95% CI, 57.4%–63.1%) women, amniocentesis for PCR diagnostics was performed. Subsequently, the data of 1189 infants (16 twin pregnancies) were analyzed, and congenital toxoplasmosis was detected in 141. In 3 dizygotic twin pregnancies, the parasite was transmitted to only 1 fetus. The infection status in all infants could be determined.

In this 17-year period, congenital toxoplasmosis incidence of 8.45 (95% CI, 7.98–8.95) PIGs per 10 000 women, and 1.0 (95% CI, .84–1.18) per 10 000 births was reported. Incidence of symptomatic congenital toxoplasmosis was 0.12 per 10 000 live births. This resulted in a mean transmission rate of 13%. In detail, the transmission was <9% (95% CI, 2.9%–14.2%)
for maternal infections during the first trimester, 21% (95% CI, 16.3%–25.7%) for the second trimester, and 45% (95% CI, 35.3%–55.3%) in the third trimester.

Due to serological course, the time point of infection according to the trimester was determined in 40.8% (95% CI, 38.0%–43.7%) of women, and in 33% (95% CI, 30.5%–35.9%) according to the exact week of gestation. An estimated 49 (13%) maternal infections occurred before week 8 of gestation and 24 (6%) after week 32 of gestation. The median time interval between seronegative and seropositive test results (seroconversion) was 14 weeks. In 14 of 141 (10%) infected infants, the serological diagnosis was performed at birth. Congenital toxoplasmosis was confirmed in 141 cases, resulting in a morbidity of 1.4% (95% CI, 0.8%–2.27%) and mortality of 0.6% (95% CI, 0.24%–1.20%). One hundred seventeen of 141 (83%) infected infants were clinically asymptomatic during the first year of life, and 93 mothers of these 117 infants (79%) were treated according to the Austrian treatment scheme and showed significantly reduced transmission of <8.6% (P < .001) in the univariable logistic regression model (Table 1). In the untreated group (n = 63), more than half of women transmitted the parasite to their fetus. In 24 of 63 untreated women (38.1%, 95% CI, 26.1%–51.2%), the infection was detected at birth, and in the remaining 39 (61.9%, 95% CI, 48.8%–73.9%), the infection was detected at a mean of 28 (SD, 9) weeks of gestation. Maternal diagnosis and treatment data in the infected and noninfected infant groups are shown in Table 2.

Figure 1 shows the increase of transmission probability during pregnancy depending on the week of gestational age at seroconversion and applied treatment scheme, based on regimen-specific median duration and initiation of treatment within 4 weeks after maternal infection. For instance, transmission risk at week 20 of gestational age was 5%, 27%, and 48% for the Austrian scheme, other regimens, and no treatment, respectively. These risks correspond to the number of women needed to treat (NNT) to avoid 1 case of congenital toxoplasmosis, equal to 2 for the Austrian scheme and 5 for other regimens. Our findings revealed a significant therapeutic effect, with a 20 times increased risk of transmission without treatment (adjusted OR, 22.10; 95% CI, 7.81–62.53; P < .001), vs treatment

Table 2. Overview of Primary Gestational Infections (N = 1173)

<table>
<thead>
<tr>
<th>Diagnosis of maternal infection (GA)</th>
<th>Crude OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.9 (25.9–34.6); 138</td>
<td>1.18 (1.15–1.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>18.4 (13.0–26.7); 1026</td>
<td>1.22 (1.17–1.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>106</td>
<td>1.12 (1.04–1.21)</td>
<td>.004</td>
</tr>
<tr>
<td>Therapy delay&lt;; wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 wk, No.</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>4 to &lt;8 wk, No.</td>
<td>1.36 (.68–2.73)</td>
<td>.39</td>
</tr>
<tr>
<td>≥8 wk, No.</td>
<td>1.38 (.33–5.72)</td>
<td>.66</td>
</tr>
<tr>
<td>Duration of maternal treatment, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0 (4.3–11.4); 109</td>
<td>0.94 (.22–4.08)</td>
<td>.93</td>
</tr>
<tr>
<td>Austrian scheme</td>
<td>0.61 (.07–5.41)</td>
<td>.66</td>
</tr>
<tr>
<td>Other regimens</td>
<td>0.82 (.78–.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No treatment, No.</td>
<td>0.99 (.90–1.09)</td>
<td>.49</td>
</tr>
</tbody>
</table>

Data are presented as median (quartiles); No. of valid cases unless otherwise specified.

Abbreviations: CI, confidence interval; GA, gestational age; OR, odds ratio.

a Effect for women treated with the Austrian scheme.
b Effect for women treated with other regimens.
c Interval between diagnosis and start of treatment.
according to the Austrian scheme with a median duration and initiation of treatment within 4 weeks after maternal infection. By comparing the Austrian scheme to other treatment regimens, the effect on the risk for fetal infection resulted in a 3-fold increase for congenital toxoplasmosis (OR, 3.00; 95% CI, 1.13–7.94, \( P = .027 \)).

**DISCUSSION**

The Austrian Toxoplasmosis Register reveals a decrease of the incidence of congenital toxoplasmosis since the implementation of the mandatory prenatal screening compared with historical data. Prior to screening, the rate of congenital toxoplasmosis was 78 per 10 000 live births [33]. In the 17-year study period, we observed a decrease of congenital toxoplasmosis to 1 per 10 000 births. In addition, we found 9 per 10 000 PGI per year. The goal of *Toxoplasma* screening is to prevent maternofetal transmission. An overall transmission rate of 13% was revealed based on the register. Our data showed that the transmission was reduced to <10% for those cases treated according to the Austrian scheme and that 86% of all women were compliant. Furthermore, our findings revealed that other treatment regimes resulted in significantly higher transmission rates of approximately 20%, and up to 50% without any treatment, respectively. Interestingly, the impact of treatment on transmission rate was higher than observed according to other programs. Hereby, a transmission rate of 25% was reported in a local study performed in France, another nation with prenatal screening but a different treatment protocol [20]. The rate observed in France was higher even though a monthly testing interval for seronegative women (bimonthly testing in Austria) was introduced. Furthermore, in our Austrian cohort, infected infants had 4% fewer clinical manifestations compared with French-treated infants, and 12% fewer in comparison to the untreated historical group [34, 35]. In summary, our data revealed that the Austrian treatment scheme resulted in a 6-fold decrease in transmission compared with women who did not receive or who did not comply with treatment. This rate would be theoretically even higher (up to a factor of 20), considering the 4-week delay between infection and therapy according to our statistical model (Figure 1). Furthermore, we assessed the effectiveness of treatment by the NNT to prevent 1 infected infant. The NNT was 2 with the Austrian treatment scheme, and 5 with other regimens, respectively.

In addition to the benefit of the Austrian treatment scheme revealed by our study, the data also suggest that prenatal screening should routinely test all pregnant women for *Toxoplasma*-specific antibodies as the majority of women with PGI are asymptomatic and do not have conventional risk factors such as contact with cats or the consumption of raw meat. Our study showed that <4% of women were identified by clinical symptoms or risk factors associated with acute infection. Therefore, only serological screening identified the majority of infected women. Even though compliance with the screening program is very high (93%) in Austria, it is important to optimize the current screening [21]. In a previous study, we showed that only 11% of all women had a first serology performed early in pregnancy [21]. Moreover, approximately 1.4% of pregnant women with chronic infection had false-negative serological results followed by unnecessary tests during pregnancy. In contrast, 0.4% of susceptible women showed false-positive serology, and these women had a risk of unidentified infection and transmission during pregnancy [21]. Misdiagnosis of congenitally infected infants might have occurred due to false-negative serological test results (up to 18%) [36, 37]. Amniotic fluid PCR is only used as a confirmatory test, with an estimated false-negative rate of 0.5% in the Austrian population (unpublished data). However, only early serological testing allows the discrimination between pre- and postconceptional infections. This is of clinical importance because only women with PGI need treatment. A recent study showed that periconceptional infections might lead to congenital toxoplasmosis [38]. In Austria, we provided a serological follow-up of infants after maternal periconceptional infections. Our data showed that all of these monitored infants were ultimately noninfected.

Our findings revealed 0.6% mortality of infected fetuses, and morbidity of live-born infants was 1.4%. These data stress the
clinical relevance of disease burden, and consequently additional standardized preventive measures are required [39].

In general, a current limitation of the screening is that not all seronegative and consequently susceptible women had serology at birth. This may lead to unidentified seroconversions.

In summary, our data demonstrated that the Austrian screening program and treatment strategy in women with PGI is an effective measure to reduce congenital toxoplasmosis. A database containing clinical records and interventions compiled during pregnancy and childhood is essential to monitor prevalence of disease and to provide data for healthcare providers.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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