Risk of Recurrence of Preexisting Ocular Toxoplasmosis during Pregnancy*

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ABSTRACT

Purpose: Comparison between the risk of recurrence during pregnancy with nonpregnant periods in patients with ocular toxoplasmosis (OT).

Methods: Records of 40 women were retrospectively reviewed. The women were subdivided into either a pregnant group or a control group formed by nonpregnant women during follow-up. Comparable cases from the literature were added. Mean number of recurrences per year was compared.

Results: Eleven women with pregnancies could be included. Six cases from the literature were added (total n = 17). Mean number of recurrences per year during versus not during pregnancy was 0.16 (SD 0.39) versus 0.32 (SD 0.30; p = 0.088), respectively. In the control group (n = 29) the mean number of recurrences per year (0.31; SD 0.27) was significantly higher when compared to cases during pregnant periods (p = 0.002).

Conclusion: Adding to published series, the presented data do not provide evidence for a relevant impact of pregnancy on recurrence behavior in OT.

Keywords: Ocular toxoplasmosis, posterior uveitis, pregnancy, prognosis, uveitis

Ocular toxoplasmosis (OT) is the leading cause of posterior uveitis in the world.1–5 It is characterized by frequent reactivations due to tissue cysts remaining in the retina after initial infection with the protozoan Toxoplasma gondii (T. gondii).6,7 Patients with OT seem to possess a lifetime risk of recurrence and therefore a permanent risk of vision loss.

Despite of the danger of vision loss, which is associated with recurrences rather than with initial infection of OT,8 curative treatment is not yet available.9 The defense against T. gondii is primary regulated by the T-cell-mediated immune response and seems to influence the course of disease.10 Hence, severe and ongoing attacks of OT occur more often in patients with decreased cellular immunity caused by the acquired immune deficiency syndrome (AIDS),11–14 long-term immunosuppression,15,16 or senescence of the infected host.17,18

A partial suppression of cell-mediated immunity is also developed in pregnancy in order to facilitate the survival of the semiallogeneic fetus. Therefore, some latent ocular diseases such as uveitis may benefit from the partial suppression of the cell-mediated immunity, while others such as infections tend to worsen during pregnancy.19,20 Especially, infections with cytomegalovirus or the human herpes virus 6 seem to reactivate more frequently during pregnancy.21,22

Concerning the risk of recurrence of OT during pregnancy a more frequent reactivation has also been suspected.5,8,23–25 However, the existing studies did not incorporate a control group. Therefore, pregnancy as a factor potentially predisposing for a higher risk of recurrence has never been examined by valid statistical methods.

Routine ophthalmological examinations of pregnant women with preexisting OT might be necessary.

*We presented the results of this study at the AUS meeting, May 2013 in Seattle, Washington.
To analyze the influence of pregnancy on the risk of recurrence we designed this retrospective case-control study with follow-up examination.

PATIENTS AND METHODS

Study Design

This was a retrospective comparative case series with follow-up examination approved by the Local Ethical Committee and adhering to the tenets of the Declaration of Helsinki.

Used Definitions, Outcome Measure, and Sample Group

For our study we used a database of 4381 patients with uveitis. All patients consulted our Interdisciplinary Uveitis Center, University of Heidelberg, between January 2000 and June 2012. Fifty-seven women could be detected who met the following inclusion criteria: (1) a signed informed consent for participation, (2) reliably diagnosed OT by clinical and, in some cases, serological criteria, (3) no long-term immunosuppression, and (4) clinically verified course of disease. For reconstructing the course of disease of the 57 women, definitions for a recurrence based on criteria by Holland et al. were used. All 57 women were followed up at least once a year and more often when suffering a recurrence. As in the study of Holland et al. for subjects with bilateral disease, only data for first-affected eyes were used in the data analysis. To investigate the risk of recurrence during pregnant and nonpregnant periods, mean number of recurrences per year was calculated. To create comparable times of follow-up among study subjects, we had to exclude 29.8% (n = 17) of the 57 women for data analyses because they were followed-up less than 4 years during childbearing age. Childbearing age was set between 15 and 45 years. The remaining 40 women constituted the data set for this study (sample group). None of those women were pregnant during their first active lesion (primary OT). Dates of deliveries during follow-up were documented; abortions were not documented.

The 40 women were subdivided into either our own cases formed by women being pregnant during follow-up (27.5%; n = 11), or the control group formed by women not being pregnant during follow-up (72.5%; n = 29). The period of pregnancy was defined with 266 days (38 weeks; 0.73 years) describing the mean period between conception to birth. Due to the retrospective nature of this study it was not possible to clinically verify the period of breastfeeding; therefore, this period was not assigned to the period of pregnancy.

Used Data from the Literature

To get a larger sample size of pregnant women a literature research was conducted. To ensure data comparability, only studies were included that (1) describe the complete clinical histories of women with preexisting OT getting pregnant during follow-up, (2) describe all cases of women in an observed series regardless OT reactivated during pregnancy or not, or (3) were carried out in countries with comparable environmental conditions as well as social structures and predominating strains of T. gondii as being present in Germany/Europe.

Only one study in the literature, by Oniki, fulfilled all these criteria. Six cases of this study were added to our own 11 cases, thus forming a case series of n = 17. Four cases of the data set of Oniki were not included in our study, those 4 cases never having been presented to an ophthalmologist with an active lesion of OT (n = 1; case 4) or they met exclusion criteria such as medically induced abortions (n = 2; cases 1 and 8) or total follow-up during childbearing age less than 4 years (n = 1; case 6). To ensure the data comparability of the 6 included cases with our own cases, statistical discrepancies in mean follow-up, mean age at the time of the initial diagnosis of OT or at the time of delivery, as well as mean number of recurrences and mean number of recurrences per year were analyzed.

Statistical Methods

SPSS version 20.0 was used for statistical analyses. For the descriptive data analysis means, standard deviation (SD), median values and minimal and maximal values were calculated. Mann-Whitney U test and Wilcoxon signed-rank test were used where appropriate. A probability (p) value of α < 0.05 was considered significant.

RESULTS

Sample Group

The sample group comprised 40 women with a mean follow-up of 13.6 years (SD 9.2 years, range 4.1–46.8 years). The mean age at the time of the initial diagnosis was 20.9 years (SD 8.5 years; range 6.7–39.2). In total, 153 recurrences were detected with a mean of 3.8 recurrences per patient (SD 4.5; median 3; range 0–27). The mean number of recurrences per year was 0.30 (SD 0.23; range 0.00–0.99).
Control Group

The control group was formed by 29 women (72.5%) of the sample group. None of the 29 women got pregnant during follow-up. The 29 women were followed-up a mean of 13.5 years (SD 9.8 years). The mean age at the time of the initial diagnosis of OT was 21.1 years (SD 8.3 years; range 8.9–39.2 years). In total, 110 recurrences were detected with a mean of 3.8 recurrences per patient (SD 5.0; median 3; range 0–27).

Our Cases

Eleven women (27.5%) of the sample group got pregnant during follow-up. In total 16 pregnancies were detected (range 1–3). Only 2 of these pregnancies of 2 different women were associated with a recurrence of OT (one occurred in the second and the other in the third trimester). In the second week after delivery another recurrence was detected. This recurrence was not included to the period of pregnancy because of not meeting the definition of the period of pregnancy defined in this study. Other than that, no more recurrences were detected in the first 6 months postpartum. The complete clinical history of the 11 women with pregnancy during follow-up is shown in Table 1.

Comparability of the Data Extracted from Literature

Six cases of the study of Oniki fulfilled all our inclusion criteria. Data from this study (n = 6) compared well to our own cases (Table 2). Therefore, the cases extracted from the literature could be added, forming a total case series of 17 patients.

Differences in Host Factors

To evaluate a possible influence of discrepancies in host factors between cases with pregnancies compared to the control group, the same host variables were evaluated as in Table 2. None of the considered host factors showed differences between cases compared to the control group (p = 0.617–0.811).

Influence of Pregnancy on the Risk of Recurrence

To analyze the difference between the risk of recurrence during the pregnant and the nonpregnant period, only data acquired during years of childbearing age were used. Table 3 summarizes the results of this analysis. When comparing the number of recurrences per year during pregnancy with the number of recurrences per year not during pregnancy the difference, although lower (0.16 versus 0.32), did not reach statistical significance ([1] p = 0.088; Table 3). However, when the number of recurrences per year during pregnancy in the case series was compared with the number of recurrences per year in the control group, the number of recurrences was significantly lower ([2] p = 0.002; Table 3). Thus, there does not seem to be an impact of pregnancy on recurrence behavior in OT.

DISCUSSION

We retrospectively analyzed the influence of pregnancy on the risk of recurrence by using a control group of nonpregnant women with OT and a follow-up while the patients are of childbearing age of more than 4 years. This was enabled by clinically verifying the course of disease of women with OT in our database regardless of being pregnant during follow-up or not. Comparing the number of recurrences per year during pregnancy with the number of recurrences per year in the control group, we could show data indicating that the risk of recurrence of OT is not increased during pregnancy (Table 3). This is in contrast to studies that suspected more frequent reactivations during pregnancy. However, all these reports show methodological limitations: the total number of patients with pregnancies, or the number of recurrences per year during the nonpregnant period was either not examined or not described. The only study demonstrating the complete clinical history of all 10 pregnant women was published by Oniki. However, the influence of pregnancy on the risk of recurrence was not topic of this study. The largest series with 18 women was presented by Garweg et al.; Braakenburg and Rothova described 9 women.

None of the studies we found used a control group. Consequently, a statistical comparison between the risk of recurrence during pregnant and nonpregnant periods has not been published before. Being of retrospective nature, with the natural limitation of data quality, the comparison we did here has to be regarded with caution. The mean numbers of recurrences show high standard deviations with overlap. Still, no significant difference between the numbers of recurrences per year during pregnant compared to nonpregnant periods could be determined in this study (Table 3). Maybe with a larger sample size a significant difference could be shown, as indicated by the seemingly lower numbers during pregnancy. Therefore, we decided to present the complete clinical history of pregnant women with OT in the cohort of the Interdisciplinary Uveitis Center, University of Heidelberg (Table 1). Hopefully, following studies
will be able to incorporate our data set, leading to a larger sample size and enable a further evaluate the differences in the risk of recurrence between pregnant and non-pregnant periods.

One could discuss that our study should have included the postpartal period or even the whole time during which women were breastfeeding. We decided to define the date of birth as the end of the period of pregnancy, as there are reports indicating that the immune system after giving birth returns to the prepregnancy status very quickly, leading to similar rates of uveitis flares.\textsuperscript{20,35} An additional factor was the lack of reliable data on breastfeeding. To ensure the consistency of our results, we recalculated our data including an additional 8 weeks postpartum period to the period of pregnancy, thus also including the one case of OT reactivation shortly after delivery (see case 5; Table 1). We saw unchanged results (data not shown).

The conclusions of this study are limited by its retrospective nature. For instance, the period of breastfeeding could not be clinically verified and

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time of follow-up (yrs)</th>
<th>First diagnosis of OT</th>
<th>End of follow-up</th>
<th>Active lesions</th>
<th>Delivery</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4.4</td>
<td>33.1</td>
<td>37.5</td>
<td>33.1 (R)</td>
<td>37.5</td>
</tr>
<tr>
<td>2</td>
<td>4.6</td>
<td>29.8</td>
<td>34.3</td>
<td>29.8 (POT)</td>
<td>34.3</td>
</tr>
<tr>
<td>3</td>
<td>9.0</td>
<td>6.7 (Beginning of follow-up: 23.7)</td>
<td>32.7</td>
<td>23.7 (R – during pregnancy)</td>
<td>23.8</td>
</tr>
<tr>
<td>4</td>
<td>13.6</td>
<td>23.0</td>
<td>36.6</td>
<td>23.0 (POT)</td>
<td>31.4</td>
</tr>
<tr>
<td>5</td>
<td>24.3</td>
<td>8.1 (Beginning of follow-up: 22.9)</td>
<td>47.2</td>
<td>26.7 (R – after delivery)</td>
<td>28.6</td>
</tr>
<tr>
<td>6</td>
<td>14.5</td>
<td>19.7</td>
<td>34.2</td>
<td>32.2 (R)</td>
<td>33.4</td>
</tr>
<tr>
<td>7</td>
<td>12.4</td>
<td>32.3</td>
<td>44.7</td>
<td>32.3 (R)</td>
<td>32.3</td>
</tr>
<tr>
<td>8</td>
<td>27.7</td>
<td>24.0</td>
<td>51.7</td>
<td>32.3 (R)</td>
<td>30.8</td>
</tr>
<tr>
<td>9</td>
<td>16.0</td>
<td>13.2</td>
<td>29.3</td>
<td>46.0 (R – outside childbearing age)</td>
<td>21.1</td>
</tr>
<tr>
<td>10</td>
<td>20.0</td>
<td>14.0</td>
<td>34.0</td>
<td>13.2 (POT – outside childbearing age)</td>
<td>23.0</td>
</tr>
<tr>
<td>11</td>
<td>6.1</td>
<td>19.5</td>
<td>25.5</td>
<td>14.0 (R – outside childbearing age)</td>
<td>25.5</td>
</tr>
</tbody>
</table>

R, recurrence; POT, primary ocular toxoplasmosis.
therefore was not assigned to the period of pregnancy. Also, abortions were not documented. Although it is difficult to determine retrospectively the duration of pregnancy until abortion, ideally future studies would assign these periods to the period of pregnancy. Two of our cases were lost to follow-up at the end of pregnancy, which might be a confounder. Although a prospective study would be preferable, it is quite complex, time-consuming, and costly to conduct one. So as long as this is not available, we think that our study is the best currently possible alternative.

Another point of argument could be that pregnancy is a relatively short period and pattern of recurrences of OT is not regular along time. This could introduce a bias. Another limitation is the small sample size and that we had to exclude a number of patients due to not meeting inclusion criteria, especially sufficient length of follow-up. Therefore, the study could be rightly challenged to not be sufficiently powered; this is an explorative study including only purely descriptive analysis. Due to the high number of statistical comparisons, an adjustment for multiplicity for the performed statistical tests is not feasible and the tests therefore provide no confirmatory evidence. For this reason, a power analysis as conducted for confirmatory clinical trials is not reasonable. The results of our study should be interpreted as pilot results that may help to improve future prospective research.

Despite the limitations of the study it could be shown, contrary to the previous assumption, that the risk of recurrence of OT is not increased during pregnancy. Therefore, additional ophthalmological examinations during pregnancy on women with preexisting OT seem unnecessary.

### DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

FM has been primary investigator in several industry-sponsored trials in the last 2 years (Abbott, Allergan, Esbatech, Novatis), has served on an advisory board for Allergan, and received lecture honoraria by Heidelberg Engineering.
These organizations had no role in the design or conduct of the research.
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REFERENCES


Recurrences of Toxoplasmosis during Pregnancy