Title
Recurrence Rates of Ocular Toxoplasmosis During Pregnancy

Journal
American Journal of Ophthalmology, 157(4)

ISSN
0002-9394

Authors
Braakenburg, Arthur MD
Crespi, Catherine M
Holland, Gary N
et al.

Publication Date
2014-04-01

DOI
10.1016/j.ajo.2014.01.004

Peer reviewed

Published in final edited form as:
Am J Ophthalmol. 2014 April ; 157(4): 767–773.e2. doi:10.1016/j.ajo.2014.01.004.

RECURRENCE RATES OF OCULAR TOXOPLASMOSIS DURING PREGNANCY

Dr. Arthur M.D. Braakenburg, **Dr. Catherine M. Crespi**, **Dr. Gary N. Holland**, **Mr. Sheng Wu**, **Dr. Fei Yu**, and **Dr. Aniki Rothova**
Department of Ophthalmology, VU Medical Center Amsterdam, the Netherlands (Dr. Braakenburg), the Department of Biostatistics, Jonathan and Karin Fielding School of Public Health (Dr. Crespi, Mr. Wu, Dr. Yu) and the Ocular Inflammatory Disease Center, Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine at UCLA (Drs. Holland, Yu), University of California, Los Angeles, California, USA, and the Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands (Dr. Rothova)

Abstract

Purpose—To investigate whether recurrence rates of ocular toxoplasmosis are higher during pregnancy among women of childbearing age.

Design—Retrospective longitudinal cohort study.

Methods—We reviewed medical records of all women seen at a university eye clinic (Utrecht, Netherlands) during episodes of active toxoplasmic retinochoroiditis that occurred while the women were of childbearing age (16–42 years). Each woman was sent a questionnaire requesting information regarding all pregnancies and episodes of ocular toxoplasmosis, whether or not episodes were observed at the eye clinic. Conditional fixed-effects Poisson regression was used to model incident rate ratios of recurrence during pregnant versus non-pregnant intervals, adjusted for potential confounders, including age at time of active toxoplasmic retinochoroiditis and interval since last episode of active disease, which are known to influence risk of recurrence.

Results—Questionnaires were returned by 50 (58%) of 86 women, 34 of whom had 69 pregnancies during 584 person-years of study. There were 128 episodes of ocular toxoplasmosis during the study period (6 during pregnancy). First episodes of ocular toxoplasmosis occurred between ages 9.6 and 38.5 years. Youngest age at pregnancy was 16.1 years; oldest age at childbirth was 40.9 years. Incident rate ratios for pregnant versus non-pregnant intervals were in

Correspondence to: Gary N. Holland, M.D., Jules Stein Eye Institute, 100 Stein Plaza, UCLA; Los Angeles, CA 90095-7000; uveitis@jsei.ucla.edu.

Financial Disclosure: Dr. Holland has served on Advisory Boards for the following companies: Novartis International AG; Santen, Incorporated; and Xoma Corporation. None of the other authors have financial disclosures.

Contributions of Authors:
Study design: (A.M.D.B., C.M.C., G.N.H, F.Y., A.R.).
Data collection: (A.M.D.B., A.R.).
Data management and analysis: (C.M.C., S.W.)
Data interpretation: (A.M.D.B., C.M.C., G.N.H, F.Y., A.R.).
Preparation of manuscript: (A.M.D.B., C.M.C., G.N.H, A.R.). Drs. Braakenburg and Crespi contributed equally to the preparation of this manuscript.
Review and approval of manuscript: (A.M.D.B., C.M.C., G.N.H, S.W., F.Y., A.R.).

the direction of lower recurrence rates during pregnancy, with point estimates of 0.54 and 0.75 under two different approaches, but ratios were not significantly different from the null value (p-values of 0.16 and 0.55).

Conclusions—Recurrence rates of ocular toxoplasmosis are likely not higher during pregnancy, in contrast to traditional beliefs.

Ocular toxoplasmosis is characterized by periodic recurrences of active disease.[1] It is commonly believed that women with histories of ocular toxoplasmosis are at increased risk of recurrent ocular disease during pregnancy,[2–5] although there has been little objective evidence to support that belief. The reasons that toxoplasmic retinochoroiditis lesions reactivate are unknown. It has been suggested that hormonal changes play a role in disease recurrences,[3] which might explain an association with pregnancy. Pregnancy is believed to affect other forms of uveitis as well.[6–11]

Most episodes of recurrent disease occur in people between the ages of 20 and 40 years;[2,12] for women, this time interval represents the child-bearing years. Risk of recurrent ocular toxoplasmosis during pregnancy is an especially important issue, because active toxoplasmic retinochoroiditis during pregnancy poses unique therapeutic challenges.[13] We sought to clarify the risk of ocular toxoplasmosis during pregnancy by investigating whether recurrence rates are greater during pregnancy than during non-pregnant periods in women of childbearing age.

METHODS

We performed a retrospective review of medical records for all female patients with active toxoplasmic retinochoroiditis examined at the Department of Ophthalmology of the University Medical Centre in Utrecht, the Netherlands from 1995 through 2005. Each eligible patient was sent a questionnaire asking for the dates of all childbirths, miscarriages, and known episodes of active toxoplasmic retinochoroiditis. They were specifically asked whether any episodes of active toxoplasmic retinochoroiditis occurred during pregnancy. An attempt was made to locate non-responders by telephone or through their general practitioners. Reported data were confirmed with hospital records, if available. This retrospective study was approved by institutional review boards at the University Medical Center, Utrecht, Netherlands and at UCLA prior to commencement of the study. A requirement for informed patient consent was waived for all aspects of the study. For authors in the United States, the study was in accordance with HIPAA regulations.

Women with retinochoroidal scars alone were not considered if no episodes of active retinochoroiditis were observed during the study period, even if the scars were consistent with past episodes of toxoplasmic retinochoroiditis, because such scars are non-specific, and we could not rule out other potential causes. Excluded from further analysis were those patients who were not examined during their potential childbearing years, as defined below. Extensive demographic, medical, and ophthalmic information was available about each patient from a pre-existing database maintained at the study institution.

Study Definitions

Active toxoplasmic retinochoroiditis was diagnosed on the basis of a discrete focus of retinal inflammation and necrosis, as described previously for clinical studies.[2,12,14] The presence of inflammatory cells in the anterior chamber or vitreous humor without an active retinal lesion was not considered to be an episode, for study purposes. Sites of active retinal inflammation did not have to arise from pre-existing retinochoroidal scars for inclusion in the study; such “primary” lesions, if seen at the first observed episode, may be associated

with a newly acquired infection, but are believed to result more commonly from reactivation of clinically inapparent tissue cysts, already present in the retina following a remote infection.[1] For simplicity, we refer to all episodes as “recurrences” in this article.

For study purposes, we arbitrarily defined the child-bearing years to be from age 16 years through age 42 years. We defined the duration of a pregnancy that ended in a live birth to be 266 days, based on a mean gestational age for singletons of 38.7 weeks (available at http://www.cdc.gov/Features/dsAvgPregnancyDuration), and adjusted downward slightly to account for multiple births. We defined the duration of a pregnancy that ends in a miscarriage to be 70 days, based on the fact that most miscarriages occur during the first trimester.

A study period was established for each patient in a way that captured the time interval during child-bearing years that the patient was at-risk for active toxoplasmic retinochoroiditis. Patients were considered to be at-risk for recurrence after serological confirmation of *T. gondii* infection or documentation of active retinochoroiditis or retinal scars consistent with past episodes of active retinochoroiditis. For the primary analysis (Approach 1, see description below), we defined the start of the study period as the earliest date on which the patient was known to be at-risk for recurrence or age 16 years, whichever was later. For patients with congenital disease, the study period was defined as starting at age 16 years. We defined the end date of the study period as the latest date for which information about both ocular disease and pregnancies was available or age 42 years, whichever was earlier. In our sensitivity analysis (Approach 2, see description below), we used an alternate start date for the study period, which was defined as beginning after resolution of an episode, if the study period started with an episode of active retinochoroiditis.

Data Collection and Study Analyses

The following information was collected from the pre-existing database for each included patient: age at first observed episode of toxoplasmic retinochoroiditis (and date of that episode to establish temporal relationships with all subsequent events); whether retinochoroidal scars were already present at the first observed episode; mode of initial *Toxoplasma gondii* infection (congenital vs. post-natally acquired), if known; and the presence or absence of anti-*T. gondii* IgG and IgM antibodies, if known. We recorded whether additional tests were performed on intraocular fluids to confirm intraocular *T. gondii* infection. Based on the questionnaires, we determined for each included patient the total number of pregnancies (and dates for each); whether each pregnancy resulted in a live birth or miscarriage; and the total number of known episodes of active toxoplasmic retinochoroiditis (and dates for each), whether or not the episode had previously been observed and entered into our existing database.

In our primary analysis (Approach 1), each patient’s study period was divided into pregnant and non-pregnant at-risk intervals and the unadjusted rate of recurrence during pregnancy was calculated as number of recurrences that started during a pregnancy divided by total duration of pregnant at-risk intervals; the unadjusted rate of recurrence during non-pregnant at-risk intervals was calculated in a similar manner. We removed the durations of episodes of active retinochoroiditis from study intervals, based on the assumption that patients are not at-risk for a recurrence during an active episode.

As a sensitivity analysis (Approach 2), we repeated the calculations using the alternate start date for the study period, as defined above. The motivation for this alternative was to avoid inflating the rate of recurrence during non-pregnant at-risk intervals. Most first episodes occurred while patients were not pregnant, and at younger ages by definition, but the period

of risk before these attacks was unknown and not included; thus, the rate of recurrence during non-pregnancy periods could be inflated by starting the study interval at the time of first episode. Confounding by younger age was also possible.[14]

Multivariate analysis was conducted in order to compare rates of recurrence during pregnant and non-pregnant at-risk intervals, adjusting for potential confounders, including patient age at the time of recurrence and interval since last episode of active retinochoroiditis.[14] As additional determinations of sensitivity, we repeated the analyses omitting each patient, to assess for undue influence, and omitting those patients known to have congenital disease.

Statistical Techniques

The Wilcoxon matched-pair signed rank test, a nonparametric analogue of the paired t-test, was used to test the hypothesis that the unadjusted rate of recurrence was the same during pregnant and non-pregnant at-risk intervals.

Because the dependent variable was a rate (number of episodes per unit time during pregnant and non-pregnant at risk intervals), Poisson regression was used to conduct adjusted analysis. Effects of predictors were expressed as incident rate ratios, which provide the estimated multiplicative change in the event rate when the predictor is increased by one unit. To conduct these analyses, the study period for each patient was broken into sub-intervals associated with different values of predictor variables, creating multiple "observations" per patient, and a conditional fixed-effects Poisson regression was used. This technique utilizes within-individual differences to estimate effects; each patient was used as her own control, and all time-stable characteristics (age at onset of infection and mode of acquisition) were automatically controlled for, and thus, did not need to be entered into the model. This feature is a major advantage of the technique, as it controls for both measured and unmeasured time-stable variables that could be confounding factors. These models are appropriate for estimating the effect of time-varying characteristics, including pregnant/non-pregnant status, which was our main characteristic of interest. As control variables, we included average age during the sub-interval and years since last episode of active retinochoroiditis, calculated with reference to average age during the sub-interval. We also repeated the analyses using random effects Poisson regression and negative binomial regression.

A p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 86 women with one or more episodes of active toxoplasmic retinochoroiditis during child-bearing years had been seen at our institution during the years covered by our dataset. Of these 86 women, 50 (58%) responded to the questionnaire and were included in this study. The earliest pregnancy among study participants occurred at age 16.1 years; the oldest age at which childbirth occurred was 40.9 years.

Characteristics of the study participants are shown in Table 1. The mean age at first documented episode of active retinochoroiditis (25.4±7.3 years) was early in the child-bearing period. First documented episodes occurred before age 16 years in 7 patients (14%). In a large proportion of patients (n=39, 78%), the first observed episode of active retinochoroiditis arose from a pre-existing retinochoroidal scar, indicating an earlier infection. None of the study participants had been treated with long-term anti-parasitic drug therapy as secondary prophylaxis to prevent future recurrences.

The median time over which histories of toxoplasmic retinochoroiditis and pregnancies was collected was 15 years (range 2.5–40.8 years). When these times were confined to the known pregnant/non-pregnant at-risk intervals, the median study period was 11.7 years (range 0.3–26 years). The total study period for all patients was 584 person-years; 44.8 of these person-years were during a pregnant state.

The number of recurrences during study periods ranged from 0 for 2 patients to 11 for 2 patients. The total number of recurrences during study periods over all patients was 128; 6 of these recurrences began during pregnancies. All episodes of recurrent toxoplasmic retinochoroiditis reported by study participants had been seen by an ophthalmologist, with documentation in medical records. In 6 cases, diagnosis was confirmed by study of aqueous humor (five with evidence of intraocular anti-*T. gondii* antibody production and one with evidence of parasitic DNA using polymerase chain technique). There were no documented recurrences during a pregnancy that resulted in miscarriage.

The unadjusted recurrence rates during pregnant and non-pregnant at-risk intervals are shown in Table 2. A total of 34 included patients had at least one pregnancy ending in either live birth or miscarriage during their study periods. In unadjusted analysis, recurrence rates were significantly lower during the pregnant at-risk intervals. Mean recurrence rates during pregnant at-risk intervals were 0.22±0.67 and 0.14±0.54 episodes/year under Approaches 1 and 2 respectively, while mean recurrence rates during non-pregnant at-risk intervals were 0.47±0.96 and 0.17±0.17 episodes/year respectively (p-values <0.05 for both approaches).

Results of the conditional fixed-effects Poisson regression analyses are provided in Table 3. The two approaches gave similar results for the effect of pregnancy on recurrence rate. Point estimates for incident rate ratios for pregnant versus non-pregnant at-risk intervals were 0.54 and 0.75, for Approaches 1 and 2 respectively, which can be interpreted as a recurrence rate that is 25%–46% lower during pregnancy; however, the incident rate ratios were not significantly different from the null value (both p-values ≥0.16).

In both Approach 1 and 2, greater interval since last episode of active retinochoroiditis was associated with decreased recurrence rate (both p values <.001), with a 90% decrease in recurrence rate for a 1-year increase in duration with Approach 1 and a 74% decrease with Approach 2. Older age was associated with increased recurrence rate in Approach 2 but not in Approach 1; the difference may be due to the inflation of recurrence rates at young ages under Approach 1.

Repeating the analyses using random effects Poisson regression and negative binomial regression gave similar results to those presented above. Analyses omitting patients one at a time did not identify any unduly influential individuals. Analyses omitting patients with congenital disease also did not substantially alter the results. Data for these various sensitivity analyses are not shown.

DISCUSSION

Several investigators have noted an association between pregnancy and recurrences of toxoplasmic retinochoroiditis.[4,5,12,15] It has been hypothesized that the relationship between pregnancy and intraocular inflammation is attributable to hormonal or immunological changes that are known to occur during pregnancy.[3,9] Reactivation of various latent infections has been reported to occur in pregnant women,[16–18] which may be related to a partial suppression of the immune system during pregnancy that prevents rejection of the fetus.[16] Severe ocular toxoplasmosis has been associated with other immunodeficiency states, including human immunodeficiency virus disease and use of immunosuppressive

drugs.[19–21] In contrast to these conditions, however, the immunodeficient state associated with pregnancy is primarily a local phenomenon of immune privilege.[22,23]

Our results do not support the common belief that recurrence rates for ocular toxoplasmosis are higher during pregnancy. Using unadjusted analyses, recurrence rates during pregnancy were significantly lower than during non-pregnant periods. Rates were also lower in our adjusted analyses, although the differences were not statistically different.

There are also many reports about the course of non-infectious uveitis during pregnancy.[6–11] Typically, they have found reduced levels of intraocular inflammation, especially during the later stages of pregnancy.[11] These findings may be relevant to ocular toxoplasmosis as well. Although retinal lesions that reactivate are believed to contain parasites, the relative contribution of productive infection versus the inflammatory response to parasitic (and possibly autoimmune) antigens in the pathogenesis of recurrent toxoplasmic retinochoroiditis lesions is not well understood.[2] One school of thought holds that the predominant disease mechanism in recurrent lesions is an inflammatory reaction to parasite antigens, either in response to antigen released with tissue cyst break-down, but without parasite reactivation and proliferation, or during very brief periods of parasite proliferation, before host defenses drive the parasites back into tissue encystment. Although the relative immunodeficient state of pregnancy might facilitate proliferation of parasites, it is also possible that it dampens the intraocular inflammation that characterizes ocular toxoplasmosis, resulting in subclinical disease, and accounting for the lower recurrence rates seen in our study.

Considering the fact that toxoplasmic retinochoroiditis is widely considered to be the most common retinal infection world-wide, there are relatively few reports describing recurrent toxoplasmic retinochoroiditis as a problem among pregnant women.[4,5,12,15,24–26] Why then has the clinical impression been so strong through the years that the risk of recurrent ocular toxoplasmosis is higher during pregnancy? Pregnancy occurs during a finite period of life, when the age-specific prevalence of ocular toxoplasmosis is believed to be highest anyway,[2,12] yet clinicians have likely compared the incidence of ocular toxoplasmosis among pregnant women to that in the general population that includes all age groups. Furthermore, one perhaps thinks of pregnancy as a single event in time, when in fact it spans an interval equal in duration to multiple typical episodes of active toxoplasmic retinochoroiditis; thus, one might attribute a falsely high incidence to ocular toxoplasmosis when it does occur at some point during pregnancy. Also, assumptions about ocular toxoplasmosis and pregnancy may simply reflect ascertainment or recall bias, because of its difficulty as a management problem, and because women are likely to be monitored more frequently for ophthalmic problems during pregnancy.

The issue under investigation is a difficult one to study, particularly with regard to defining periods at-risk, both for pregnant and non-pregnant women. These difficulties raise the possibility of flaws in our study design. The fact that we tested two models with different assumptions, both of which resulted in similar conclusions, makes us comfortable that we have addressed the problem appropriately. There could, of course, be problems with our dataset that would affect results with any study design. We doubt that there are inherent problems with our master dataset, however, as similar datasets of patients with ocular toxoplasmosis from the same institution have been used in previous studies that produced biologically plausible results,[12,14] many of which have been confirmed by other investigators.

Our study has the limitations of a retrospective study, including the potential for response and recall bias. The response rate to our questionnaire was only 58% (50 of 86 potential

participants), which may, in part, be a reflection of the mobility that characterizes a young urban patient population. Nevertheless, our primary model found the same relationships identified in a previous investigation that used the entire population from which the current study patients were drawn, which supports the quality of our results; specifically, risk of recurrence increased with age of the patient and decreased with interval since last episode of active disease.[14]

Those responding to the questionnaire may not represent all women with ocular toxoplasmosis who have been pregnant. If there was a response bias, however, one might expect women who experienced ocular toxoplasmosis during pregnancy to be more likely to respond than those who did not, thereby falsely increasing recurrence rates, which was not our finding. It is also possible that not all episodes of ocular toxoplasmosis were identified. To have missed a higher recurrence rate during pregnancy, we would have to have missed episodes during reported pregnancies, yet these episodes would be the least likely to have been overlooked, because of the greater medical attention provided women during pregnancy.

True recurrence rates might be masked by confounders related to pregnancy that were not considered in the analyses. We did restrict analyses to the age range during which pregnancy is most likely to occur. We also accounted for potential changes in risk of recurrence that are associated with age and duration since last active episode of ocular disease, factors that are known to influence risk.[14] Based on our current understanding of the disease, we are unaware of other confounders that would likely have influenced disease differentially in our comparison groups. Thus, although the relatively small sample size limited statistical power to detect all effects, we are confident that our study has not missed a substantial difference in risk of recurrent toxoplasmic retinochoroiditis between pregnant and non-pregnant women.

We did not assess the risk of first episodes of ocular disease during pregnancy among *T. gondii*-infected women without histories of ocular toxoplasmosis. Most episodes of ocular toxoplasmosis in adults represent recurrent lesions,[1,2,12] and thus, we have studied the most relevant subset of infected women in terms of eye disease.

In summary, our results do not support the common belief that pregnancy makes women more susceptible to recurrence of toxoplasmic retinochoroiditis. The most appropriate interpretation of results is based on our primary analysis (Approach 1); Approach 2 was a sensitivity analyses conducted mainly to assess potential bias in the primary results, due to the fact that the study period for most women started with an episode during a non-pregnant interval. By design, Approach 2 should bias the results towards higher risk estimates during pregnant vs. non-pregnant intervals. Our primary analysis does not prove a lower recurrence rate during pregnancy, and we cannot rule-out the possibility that the rate is, in fact, higher during pregnant periods; however, the 95% confidence interval of Approach 1 (0.22–1.29) seems to exclude the possibility of an appreciable increase in risk. There is, in fact, some additional support for our observation that risk during pregnancy is similar or lower during pregnancy. A review of the clinical characteristics of ocular toxoplasmosis in our study population found no difference in the clinical features of disease between women who were pregnant and those who were not pregnant during episodes of activity.[24] If women were at increased risk of recurrence during pregnancy, one might expect that the retinal lesions they experience would be more severe, as seen among other immunodeficient patients.

There are public health and scientific implications of our results. Past reports of a higher risk of recurrent toxoplasmosic retinochoroiditis during pregnancy have been taken as presumptive evidence of a role for hormonal influences in the pathogenesis of ocular toxoplasmosis, which may not be true. Further study of this issue will be facilitated by

inclusion of information about pregnancy history among demographic and medical data collected in prospective, longitudinal clinical studies. Finally, our findings do not diminish the importance of ocular toxoplasmosis during pregnancy, when it does occur, as an important management issue.[13]

Acknowledgments

Funding: Supported by Research to Prevent Blindness (RPB), Inc., New York, NY (Dr. Holland), the Skirball Foundation, New York, NY (Dr. Holland), National Institutes of Health Grant UL1TR000124 (Dr. Crespi); the Dr. F.P. Fischer Foundation, Utrecht, Netherlands (Drs. Braakenburg, Rothova). Dr. Holland is recipient of an RPB Physician-Scientist Award. Funding entities had no role in the conduction or presentation of this study.

References

1. Holland GN. Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease. Am J Ophthalmol. Dec; 2003 136(6):973–988. [PubMed: 14644206]
2. Holland GN. Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management. Am J Ophthalmol. Jan; 2004 137(1):1–17. [PubMed: 14700638]
3. O'Connor GR. Factors related to the initiation and recurrence of uveitis. XL Edward Jackson memorial lecture. Am J Ophthalmol. Nov; 1983 96(5):577–599. [PubMed: 6139024]
4. Garweg JG, Scherrer J, Wallon M, Kodjikian L, Peyron F. Reactivation of ocular toxoplasmosis during pregnancy. BJOG. Feb; 2005 112(2):241–242. [PubMed: 15663591]
5. Kump LI, Androudi SN, Foster CS. Ocular toxoplasmosis in pregnancy. Clin Experiment Ophthalmol. Oct; 2005 33(5):455–460. [PubMed: 16181268]
6. Omoti AE, Waziri-Erameh JM, Okeigbemen VW. A review of the changes in the ophthalmic and visual system in pregnancy. Afr J Reprod Health. Dec; 2008 12(3):185–196. [PubMed: 19435022]
7. Kump LI, Cervantes-Castaneda RA, Androudi SN, Foster CS, Christen WG. Patterns of exacerbations of chronic non-infectious uveitis in pregnancy and puerperium. Ocul Immunol Inflamm. Apr; 2006 14(2):99–104. [PubMed: 16597539]
8. Schultz KL, Birnbaum AD, Goldstein DA. Ocular disease in pregnancy. Curr Opin Ophthalmol. Oct; 2005 16(5):308–314. [PubMed: 16175045]
9. Chan CC, Reed GF, Kim Y, Agron E, Buggage RR. A correlation of pregnancy term, disease activity, serum female hormones, and cytokines in uveitis. Br J Ophthalmol. Dec; 2004 88(12): 1506–1509. [PubMed: 15548800]
10. Rabiah PK, Vitale AT. Noninfectious uveitis and pregnancy. Am J Ophthalmol. Jul; 2003 136(1): 91–98. [PubMed: 12834675]
11. Chiam NP, Hall AJ, Stawell RJ, Busija L, Lim LL. The course of uveitis in pregnancy and postpartum. Br J Ophthalmol. Oct; 2013 97(10):1284–1288. [PubMed: 23887982]
12. Bosch-Driessen LE, Berendschot TT, Ongkosuwito JV, Rothova A. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. Ophthalmology. May; 2002 109(5):869–878. [PubMed: 11986090]
13. Holland GN, Lewis KG. An update on current practices in the management of ocular toxoplasmosis. Am J Ophthalmol. Jul; 2002 134(1):102–114. [PubMed: 12095816]
14. Holland GN, Crespi CM, ten Dam-van Loon N, et al. Analysis of recurrence patterns associated with toxoplasmic retinochoroiditis. Am J Ophthalmol. Jun; 2008 145(6):1007–1013. [PubMed: 18343351]
15. Friedmann CT, Knox DL. Variations in recurrent active toxoplasmic retinochoroiditis. Arch Ophthalmol. Apr; 1969 81(4):481–493. [PubMed: 5777756]
16. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. Nov; 2006 12(11):1638–1643. [PubMed: 17283611]
17. Dahl H, Fjaertoft G, Norsted T, Wang FZ, Mousavi-Jazi M, Linde A. Reactivation of human herpesvirus 6 during pregnancy. J Infect Dis. Dec; 1999 180(6):2035–2038. [PubMed: 10558965]
18. Shen CY, Chang SF, Yen MS, Ng HT, Huang ES, Wu CW. Cytomegalovirus excretion in pregnant and nonpregnant women. J Clin Microbiol. Jun; 1993 31(6):1635–1636. [PubMed: 8391026]

19. Hodge WG, Seiff SR, Margolis TP. Ocular opportunistic infection incidences among patients who are HIV positive compared to patients who are HIV negative. Ophthalmology. May; 1998 105(5): 895–900. [PubMed: 9593394]
20. Holland GN, Engstrom RE Jr, Glasgow BJ, et al. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol. Dec 15; 1988 106(6):653–667. [PubMed: 3195645]
21. Holland GN. Ocular toxoplasmosis in the immunocompromised host. Int Ophthalmol. Dec; 1989 13(6):399–402. [PubMed: 2697706]
22. Biedermann K, Flepp M, Fierz W, Joller-Jemelka H, Kleihues P. Pregnancy, immunosuppression and reactivation of latent toxoplasmosis. J Perinat Med. 1995; 23(3):191–203. [PubMed: 8568611]
23. Niederkorn JY. See no evil, hear no evil, do no evil: the lessons of immune privilege. Nat Immunol. Apr; 2006 7(4):354–359. [PubMed: 16550198]
24. Braakenburg AM, Rothova A. Clinical features of ocular toxoplasmosis during pregnancy. Retina. May; 2009 29(5):627–630. [PubMed: 19262434]
25. Martinez CE, Zhang D, Conway MD, Peyman GA. Successful management of ocular toxoplasmosis during pregnancy using combined intraocular clindamycin and dexamethasone with systemic sulfadiazine. Int Ophthalmol. 1998; 22(2):85–88. [PubMed: 10472767]
26. Oniki S. Prognosis of pregnancy in patients with toxoplasmic retinochoroiditis. Jpn J Ophthalmol. 1983; 27(1):166–174. [PubMed: 6855010]

Biographies

Arthur M.D. Braakenburg, M.D. is an ophthalmologist who works at the Gelre Hospital in Apeldoorn, the Netherlands. He completed his residency in ophthalmology in 2013 at the Free University Medical Center in Amsterdam. His fields of interest include uveitis and glaucoma.

Catherine M. Crespi, Ph.D. is an Associate Professor of Biostatistics, Jonathan and Karin Fielding School of Public Health, University of California, Los Angeles. Her research interests include the longitudinal analysis of recurrent and chronic diseases. She collaborates widely on biomedical and disease prevention research.

Table 1

Characteristics of 50 Female Patients with Toxoplasmic Retinochoroiditis seen in Utrecht, Netherlands.

Characteristic	Value
Age at first observed episode (years)	
Mean±SD	25.4±7.3
Range	9.6 – 38.5
Laterality of toxoplasmic retinochoroiditis (n, percentage)	
Unilateral	48 (96%)
Bilateral	2 (4%)
Mode of infection (n, percentage)	
Congenital	4 (8%)
Acquired	2 (4%)
Unknown	44 (88%)
Retinal scars at initial examination (n, percentage)	
Yes	39 (78%)
No	2 (4%)
Unknown	9 (18%)
IgM anti-*T. gondii* antibodies (n, percentage)	
Positive	1 (2%)
Negative	26 (52%)
Unknown	23 (46%)
IgG anti-*T. gondii* antibodies (n, percentage)	
Positive	33 (66%)
Unknown	17 (34%)
Study periods[a] (years)	
Median	11.7
Range	0.3 – 26
Total number of episodes of active toxoplasmic retinochoroiditis during study periods	128
Total number of episodes of active toxoplasmic retinochoroiditis that began during pregnancy	6
Any pregnancies (including miscarriages) during study periods (n, percentage)	34 (78%)
Pregnancies resulting in childbirth during study periods, per patient (n, percentage)	
0	17 (34%)
1	13 (26%)
2	15 (30%)
3	5 (10%)
Pregnancies resulting in miscarriage during study periods, per patient (n, percentage)	
0	41 (82%)
1	7 (14%)
2	2 (4%)
Episodes of active toxoplasmic retinochoroiditis during study periods, per patient (n, percentage)	

Characteristic	Value
0	2 (4%)
1	20 (40%)
2	9 (18%)
3	8 (16%)
4 or more	10 (20%)

SD=standard deviation.

[a]Study period was defined as the interval during childbearing years (16–42 years of age) during which patients were at-risk for active toxoplasmic retinochoroiditis. The start date was at age 16 years for patients known to have had congenital infections; for all others, the start date was defined by the first observation of active retinochoroiditis (or retinochoroidal scars consistent with past episodes of toxoplasmosis) or age 16 years, whichever was later; the end date was at age 42 years or at last contact with patient, if younger than age 42 years.

Table 2

Comparison of Unadjusted Rates of Recurrent Toxoplasmic Retinochoroiditis for 50 Women During Pregnant and Non-pregnant At-risk Intervals.

Approach	Recurrence Rate During Pregnant At-risk Periods[a] (episodes/year)			Recurrence Rate During Non-pregnant At-risk Periods (episodes/year)			P-value[b]
	Mean±SD	Median	Range	Mean±SD	Median	Range	
1[c]	0.22±0.67	0.00	0 – 2.99	0.47±0.96	0.23	0 – 6.67	.03
2[d]	0.14±0.54	0.00	0 – 2.99	0.17±0.24	0.10	0 – 1.26	.007

SD=standard deviation.

[a] A total of 34 patients were pregnant during study periods.

[b] Wilcoxon matched-pairs signed rank test.

[c] In Approach 1, start date for each patient's study interval was defined as the earliest date on which the patient was known to be at-risk of recurrence or age 16 years, whichever was later; end date was defined as the latest date for which information regarding toxoplasmic retinochoroiditis and pregnancies was available or age 42 years, whichever was earlier.

[d] Approach 2 differs from Approach 1 in defining the start date after resolution of the first observed episode, if the study period began with an episode.

Table 3

Results of Conditional Fixed-effects Poisson Regression Results for 48 Women with Histories of Toxoplasmic Retinochoroiditis.

Characteristic	Approach 1[a,b]		Approach 2[a,c]	
	Incidence rate ratio (95% CI)	P-value	Incidence rate ratio (95% CI)	P-value
Pregnant (vs. non-pregnant)	0.54 (0.22–1.29)	.16	0.75 (0.29–1.94)	.55
Age at time of active disease (per year)	0.99 (0.93–1.06)	.87	1.14 (1.04–1.25)	.004
Interval since last episode of active disease (per year)	0.10 (0.07–0.15)	<.001	0.26 (0.19–0.35)	<.001

CI = confidence interval.

[a] Two of 50 study patients had no episodes of toxoplasmic retinochoroiditis during study periods, and were dropped from the conditional Poisson regression analysis, which requires individuals to have at least one event.

[b] In Approach 1, start date for each patient's study interval was defined as the earliest date on which the patient was known to be at-risk of recurrence or age 16 years, whichever was later; end date was defined as the latest date for which information regarding toxoplasmic retinochoroiditis and pregnancies was available or age 42 years, whichever was earlier.

[c] Approach 2 differs from Approach 1 in defining the start date after resolution of the first observed episode, if the study period began with an episode.