Recurrence Rates of Ocular Toxoplasmosis During Pregnancy

ARTHUR M.D. BRAAKENBURG, CATHERINE M. CRESPI, GARY N. HOLLAND, SHENG WU, FEI YU, AND ANIKI ROTHOVA

• PURPOSE: To investigate whether recurrence rates of ocular toxoplasmosis are higher during pregnancy in 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 incidence rate ratios of recurrence during pregnant versus nonpregnant 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 for recurrence.
• RESULTS: Questionnaires were returned by 50 (58%) of 86 women, 34 of whom had 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. The youngest age at pregnancy was 16.1 years; the oldest age at childbirth was 40.9 years. The incidence-rate ratios for pregnant versus nonpregnant intervals were in the direction of lower recurrence rates during pregnancy, with point estimates of 0.54 and 0.75 under 2 different approaches, but the ratios were not significantly different from the null value (*P* values of 0.16 and 0.55).
• CONCLUSIONS: Recurrence rates of ocular toxoplasmosis are probably not higher during pregnancy, in contrast to traditional beliefs. (Am J Ophthalmol 2014;157:767–773. © 2014 by Elsevier Inc. All rights reserved.)

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From the Department of Ophthalmology, VU Medical Center Amsterdam, the Netherlands (A.M.D.B.); the Department of Biostatistics, Jonathan and Karin Fielding School of Public Health, UCLA, Los Angeles, California (C.M.C., S.W., F.Y.); the Ocular Inflammatory Disease Center, Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, California (G.N.H., F.Y.); and the Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands (A.R.).

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

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 for recurrent ocular disease during pregnancy,[2–5] although there has been little objective evidence to support that belief. The reasons 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 childbearing years. Risk for 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 for ocular toxoplasmosis during pregnancy by investigating whether recurrence rates are greater during pregnancy than during nonpregnant 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 nonresponders 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. The requirement of informed patient consent was waived for all aspects of the study. For authors in the United States, the study was in accordance with Health Insurance Portability and Accountability Act regulations.

Women with retinochoroidal scars alone were not considered if no episodes of active retinochoroiditis were

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observed during the study period, even if the scars were consistent with past episodes of toxoplasmic retinochoroiditis, because such scars are nonspecific, and we could not rule out other potential causes. Excluded from further analysis were 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 childbearing years to extend from 16 years of age through 42 years of age. 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 we adjusted it downward slightly for multiple births. We defined the duration of a pregnancy that ended 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 childbearing years when the patient was at risk for active toxoplasmic retinochoroiditis. Patients were considered to be at risk for recurrence after serologic confirmation of *Toxoplasma 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 16 years of age, whichever was later. For patients with congenital disease, the study period was defined as starting at 16 years of age. 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 42 years of age, whichever was earlier. In our sensitivity analysis (approach 2; see description below), we used an alternative start date for the study period, which was defined as beginning after the 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 so as to establish temporal relationships with all subsequent events); whether retinochoroidal scars were already present at the first observed episode; the mode of initial *T. gondii* infection (congenital vs postnatally 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 nonpregnant 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 nonpregnant 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 alternative start date for the study period, as defined above. The motivation for this alternative was to avoid inflating the rate of recurrence during nonpregnant at-risk intervals. Most first episodes occurred while patients were not pregnant and of younger age, by definition, but the period of risk before these attacks was unknown and was not included; thus, the rate of recurrence during nonpregnancy 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 nonpregnant 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 while omitting each patient so as to assess for undue influence and while omitting 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 nonpregnant at-risk intervals.

Because the dependent variable was a rate (number of episodes per unit time during pregnant and nonpregnant