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CLINICAL STUDY

Commercial laboratory IgM testing for *Toxoplasma gondii* in pregnancy: A 20-year experience

DAVID J. GARRY, ANDREW ELIMIAN, VANDY WIENCEK, & DAVID A. BAKER

Department of Obstetrics, Gynecology and Reproductive Medicine, Stony Brook University, Stony Brook, NY, USA

Abstract

Objective. This study was performed to review the clinical utility of commercial laboratory *Toxoplasmosis*-specific IgM testing during pregnancy and outcomes of the gestation at our institution.

Methods. A retrospective review of all women referred for suspected acute *Toxoplasma gondii* infection during pregnancy from 1984 through 2004 was performed. Women were diagnosed with suspected acute toxoplasmosis based on commercial laboratory serologic antibody testing. All women had blood sent to a recognized reference laboratory for antibody testing within 2 weeks of the commercial laboratory results. The study protocol was approved by the Institutional Review Board. Chi-square analysis were used with a significance of $P < .05$.

Results. A total of 130 women were evaluated during the study period with 116 IgM positive results from the commercial laboratories. The commercial laboratory antibodies were as follows: IgM positive with IgG negative ($n = 20$), IgM positive with IgG positive ($n = 96$), and IgM negative with IgG positive ($n = 14$). There was a significant reduction in the IgM positive results when comparing commercial laboratory ($n = 116$) with the reference laboratory results ($n = 28$; $p < .001$). Acute toxoplasmosis infection was diagnosed in 7 (5%) of the women. All cases of acute toxoplasmosis infection had a positive commercial laboratory IgM result. The false positive rate for the commercial laboratory IgM was 88.6% and the diagnostic indices were sensitivity 100%, specificity 11.4%, positive predictive value 6% and negative predictive value 100%.

Conclusion. Commercial laboratory *Toxoplasmosis*-specific IgM is associated with a high false positive rate. The commercial and reference laboratory IgM results identified all cases of acute toxoplasmosis infection. Commercial laboratories reflexively obtaining reference laboratory confirmation of positive results could reduce costs associated with testing, referrals, retesting, and invasive procedures.

Keywords: *Perinatal infection, false positive, antibody*

Introduction

The seroprevalence of *Toxoplasma gondii* (toxoplasmosis) in women aged 15 to 44 years is approximately 15% [1]. The disease is not nationally reportable in the United States; however, an estimated 400 to 4000 congenital infections occur annually [2]. Vertical transmission rates increase from 10 to 15% in the first trimester to 60% in the third trimester [3,4]. The severity of disease is inversely related to gestational age with worsening sequelae occurring earlier in pregnancy. The annual economic impact of toxoplasmosis is millions in US dollars [5].

Detection of toxoplasmosis utilizing IgM antibodies is the most common method used to determine if infection has occurred. The IgM antibodies rise quickly in response to infection, but may be persistently elevated for many months [6]. A negative IgM result during pregnancy is most reassuring that acute infection has not occurred. Commercial test kits for *Toxoplasmosis*-specific IgM have been available for usage with unacceptably high false positive rates. In 1997 the United States Food and Drug Administration (FDA) issued an advisory regarding the clinical limits of the Toxoplasmosis IgM commercial test kits [7]. A recent survey of obstetrician-gynecologists demonstrated lack of knowledge to the problems associated with toxoplasmosis IgM testing [8].

The objective of this study was to review the clinical utility of *Toxoplasmosis*-specific IgM testing during pregnancy and outcomes of the gestation at our institution.

Materials and methods

The records of all women referred for suspected acute *Toxoplasma gondii* infection during pregnancy from January 1984 through April 2004 were included in

Correspondence: David A. Baker, MD, Department of Obstetrics, Gynecology and Reproductive Medicine, HSC T9, Room 030, Stony Brook University, Stony Brook, NY 11791, USA. Tel: 631 444 7650. Fax: 631 444 3944. E-mail: dbaker@notes.cc.sunysb.edu

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the study. All women were diagnosed with suspected acute toxoplasmosis based on commercial laboratory serologic antibody testing and referred for consultation. A suspected acute infection was based on elevated levels of *Toxoplasmosis*-specific IgM antibody with or without high levels of *Toxoplasmosis*-specific IgG or based on clinical history and a significantly elevated *Toxoplasmosis*-specific IgG. All women had blood sent to a recognized reference laboratory for toxoplasmosis testing (Toxoplasmosis Serology Lab, Research Institute, Palo Alto Medical Foundation, Ames Building, 795 El Camino Real, Palo Alto, CA 94301; http://www.pamf.org/serology/) within two weeks of the commercial laboratory results. Acute toxoplasmosis was suggested based on an acute pattern of additional reference laboratory testing which included Sabin-Feldman Dye test, IgA ELISA, IgE ELISA, AC/HS, and IgG avidity testing. Amniotic fluid polymerase chain reaction (PCR) examination was offered to confirm fetal involvement in all women diagnosed with acute toxoplasmosis infection that did not opt to terminate the gestation.

The study protocol was approved by the Institutional Review Board. Student *t*-test and Mann-Whitney U test were used for comparison of continuous variables and χ^2 analysis or Fisher exact test were used for comparison of dichotomous variables. Significance was considered when $P < .05$.

Results

A total of 130 women were evaluated during the study period with a mean maternal age ($\pm$ SD) of 30.4 $\pm$ 4.5 years. The mean gestational age ($\pm$ SD) was 14.0 $\pm$ 4.9 weeks, 44% ($n = 57$) referred in the first trimester and 30% ($n = 39$) nulliparous.

There were 116 *Toxoplasmosis*-specific IgM positive results from the commercial laboratories. The commercial laboratory antibodies were as follows: IgM positive with IgG negative ($n = 20$), IgM positive with IgG positive ($n = 96$), and IgM negative with IgG positive ($n = 14$). There was a significant reduction in the *Toxoplasmosis*-specific IgM positive results when comparing commercial laboratory results ($n = 116$) to the reference laboratory *Toxoplasmosis*-specific IgM results ($n = 28$; $p < .001$). There was no significant difference in the *Toxoplasmosis*-specific IgG positive results after reference laboratory testing (commercial positive $n = 110$ versus reference positive $n = 99$; $p = .11$). In the women with significantly elevated commercial laboratory IgG positive results that suggested infection, all had IgG positive results in the normal positive range from the reference laboratory with negative IgM results.

Acute toxoplasmosis infection was suggested with the additional reference laboratory testing in 7 (5%) of the women. Two of the women opted for termination of pregnancy and further confirmatory testing was not performed on the aborted products. The remaining 5 women confirmed the congenital transmission with amniotic fluid PCR and then received spiramycin therapy and no congenital toxoplasmosis infections were found. All cases of acute toxoplasmosis infection had a positive commercial laboratory IgM result. The false positive rate for the commercial laboratory *Toxoplasmosis*-specific IgM was 88.6% and the diagnostic indices were sensitivity 100%, specificity 11.4%, positive predictive value 6% and negative predictive value 100%. The false positive rate for the reference laboratory *Toxoplasmosis*-specific IgM was 17.1% and the diagnostic indices were sensitivity 100%, specificity 82.9%, positive predictive value 25% and negative predictive value 100% (Table I).

Discussion

Toxoplasma gondii remains an insidious infectious agent during pregnancy with possible vertical transmission to the fetus. In our population the incidence of acute maternal disease was 5%, however this varies by country and location. The serologic testing for *Toxoplasmosis*-specific antibodies has changed little over the 20 year course in our review.

There remains an unacceptably high false positive rate for *Toxoplasmosis*-specific IgM testing in pregnancy in the diagnosis of acute toxoplasmosis infection. Serologic testing for toxoplasmosis is not uniformly consistent in commercial laboratories and false positive results resulted in the FDA's advisory 7 years ago [7]. When initial IgM and IgG results suggest acute infection, repeat testing utilizing a well-recognized reference laboratory is recommended by the American College of Obstetrician Gynecologists [9]. Commercial laboratories do not automatically utilize a reference laboratory for confirmation of suggested acute infection. Recently, a survey demonstrated only 12% (43/364) of obstetrician-gynecologists realized that a positive *Toxoplamosis*-specific IgM test could be a false positive and only 11% (39/363) were aware of the 1997 FDA advisory regarding the false positive *Toxoplamosis*-specific IgM test [8]. There is great potential for harm when the obstetrician or other provider confers a false positive result to the patient without reference laboratory evaluation [8]. A recent advance has suggested the use of a single IgG avidity test to more accurately diagnosis suspected acute infection has been suggested [10].

The finding of a positive commercial laboratory *Toxoplasmosis*-specific IgM testing during pregnancy does have value. First, the negative commercial laboratory IgM conveys no risk for acute toxoplas-

Table I. Diagnostic indices in prediction of acute toxoplasmosis for *Toxoplamosis*-specific IgM from commercial and reference laboratories.

	Sensitivity	Specificity	PP+	PP-	Accuracy
Commercial laboratory IgM	100%	11.4%	6.0%	100%	13.8%
Reference laboratory IgM	100%	82.9%*	25%*	100%	69.2%

* $p < .05$; PP+, Positive predictive value, PP-, Negative predictive value.

mosis infection. Secondly, all cases of acute toxoplasmosis infection had commercial laboratory IgM results that were positive. Several reports have related a false immunologic reactivity to the low molecular weight antigen of *Toxoplasma gondii* which is unrelated to acute toxoplasmosis infection and misleads interpretation of results [11,12]. Commercial laboratories do not currently confirm their *Toxoplasmosis*-specific IgM positive results with any reference laboratory. Utilization of a reference laboratory is necessary to confirm a positive *Toxoplasmosis*-specific IgM positive result from a commercial laboratory. Commercial laboratories reflexively obtaining a certified reference laboratory evaluation of all positive *Toxoplasmosis*-specific IgM would be cost effective compared to the current model which includes testing, referral for consultation, retesting and invasive procedures.

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