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VIDAS Test for Avidity of *Toxoplasma*-Specific Immunoglobulin G for Confirmatory Testing of Pregnant Women

Jose G. Montoya,[1,2]* Oliver Liesenfeld,[1]† Sandra Kinney,[1] Cynthia Press,[1] and Jack S. Remington[1,2]

Department of Immunology and Infectious Diseases, Research Institute, Palo Alto Medical Foundation, Palo Alto,[1] and Department of Medicine and Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford,[2] California

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Because congenital toxoplasmosis is almost solely the result of maternal infection acquired during gestation, it is critical to determine whether infection during pregnancy has occurred. In the United States, definitive diagnosis of the acute infection and the time of its occurrence have been compromised by a lack of systematic screening and the fact that only a single serum sample is submitted for testing. In studies in Europe, and depending on the method used, the demonstration of high-avidity immunoglobulin G (IgG) toxoplasma antibodies has been shown to exclude infection having occurred in the first 3 to 5 months of pregnancy. We investigated the usefulness of determining the avidity of IgG toxoplasma antibodies with a VIDAS kit (herein referred to as the VIDAS Toxo-IgG avidity kit, the VIDAS kit essentially rules out acute infection having occurred within the 4 prior months) in the setting of a reference serology laboratory in the United States. Sera (132 samples) from 132 women in the first 16 weeks of pregnancy were chosen because at least one test in the toxoplasma serological profile (TSP) suggested or was equivocal for a recently acquired infection. High-avidity antibodies were demonstrated in 75% of 99 sera positive with the IgM enzyme-linked immunosorbent assay (ELISA) and 31.3% of 16 sera with acute TSP results. A significant percentage of sera with equivocal results wtih the IgM ELISA or TSP also had high-avidity test results. Of 39 women for whom treatment with spiramycin had been suggested to attempt to prevent congenital transmission, 19 (48.7%) had high-avidity antibodies. These findings highlight the value of the VIDAS IgG avidity kit when used in combination with the TSP to exclude recent infection, especially when only a single serum sample is available.

Tests to detect the presence of toxoplasma-specific immunoglobulin G (IgG) and IgM antibodies are most commonly used to attempt to determine in a serum sample whether a pregnant woman has acquired the acute infection during gestation (17). In the absence of systematic serologic testing during gestation (e.g., every month or trimester as performed in France), physicians in the United States most often submit only a single serum sample obtained at widely various times during pregnancy. Serologic test results in such single specimens cannot determine whether the infection was acquired during gestation; at best, the timing of the infection can only be estimated.

A low IgG titer and a negative IgM test in a pregnant woman in the first 24 weeks of gestation essentially places the acquisition of the infection prior to gestation. A positive IgM test result in a single serum sample may reflect a recently acquired infection, an infection acquired in the distant past, or a false-positive result.

A false-positive or a true-positive IgM test result erroneously interpreted can be misleading and result in unnecessary abortions (10). In a recent study, 60% of pregnant women in the United States who had positive IgM tests performed in nonreference laboratories were found to be chronically infected (10). In an attempt to rectify this situation, the U.S. Food and Drug Administration has recommended that a positive IgM test result should undergo confirmatory testing (16). In the Toxoplasma Serology Laboratory of the Palo Alto Medical Foundation (PAMF-TSL), sera with positive IgM test results undergo additional testing. Confirmatory tests at PAMF-TSL include those for detection of IgG, IgM, IgA, and IgE antibodies (referred to as the toxoplasma serological profile [TSP]) (11, 13). The TSP has proved useful to differentiate between recently acquired and distant infections.

Recently, a number of tests for the avidity of toxoplasma IgG antibodies have been introduced to help differentiate between recently acquired and distant infections (1, 3–7, 9, 15, 19). The functional affinity of specific IgG antibodies is initially low after primary antigenic challenge and increases during subsequent weeks and months by antigen-driven B-cell selection. Protein-denaturing reagents, including urea, are used to dissociate the antibody-antigen complex. The avidity result is determined by using the ratios of antibody titration curves of urea-treated and untreated samples. Studies of the kinetics of the avidity of IgG in pregnant women in whom seroconversion has occurred during gestation have shown that women with high-avidity test results have been infected with *Toxoplasma gondii* for at least 3 to 5 months (the time to conversion from low- to high-avidity antibodies varies with the method used). Because low-avidity antibodies may persist for many months, their presence does not necessarily indicate recently acquired infection.

Recently, we reported the results of testing for the avidity of

* Corresponding author. Mailing address: Research Institute, Palo Alto Medical Foundation, Ames Building, 795 El Camino Real, Palo Alto, CA 94301. Phone: (650) 853-6061. Fax: (650) 329-9853. E-mail: gilberto@leland.stanford.edu.

† Present address: Department of Medical Microbiology and Immunology of Infection, Institute for Infection Medicine, Benjamin Franklin Medical Center, Free University of Berlin, Berlin, Germany.

TABLE 1. Comparison of IgM ELISA and VIDAS IgG avidity test results for 127 serum samples from pregnant women during the first 16 weeks of gestation[a]

Avidity result	No. (%) of samples with IgM ELISA result		
	Positive (n = 99)	Equivocal (n = 8)	Negative (n = 20)
Low	14 (14.1)	0	2 (10)
Borderline	11 (11.1)	1 (12.5)	6 (30)
High	74 (74.8)	7 (87.5)	12 (60)

[a] Five sera with high background results in the IgM test titer were excluded from this analysis.

IgG in pregnant women in the first 12 weeks of gestation by using the Labsystems (Helsinki, Finland) IgG avidity enzyme immunoassay method (9). With this method, a high avidity has been stated to exclude the possibility that the infection occurred in the previous 12 weeks. Thus, its greatest value is in sera obtained from pregnant women in the first trimester of gestation.

A high-IgG-avidity test result with the more recently developed VIDAS method (available commercially in Europe) has been stated to rule out that infection occurred during the prior 4 months, thereby extending the value of avidity testing to the fourth month of gestation (15). The present study was undertaken to evaluate the role of the VIDAS Toxo-IgG avidity test along with the TSP for confirmatory testing of pregnant women during the first 16 weeks of gestation.

MATERIALS AND METHODS

Sera (132 samples) from 132 women in the first 16 weeks of gestation were studied. The sera were submitted to the PAMF-TSL between February 1996 and September 1999. The sera had routinely been tested with the TSP comprised of the Sabin-Feldman dye test (DT) (18), double-sandwich IgM enzyme-linked immunosorbent assay (ELISA) (14), IgA ELISA (20), IgE ELISA (22), IgE immunosorbent agglutination assay (ISAGA) (22), and the differential agglutination test (2). The Sabin-Feldman DT is considered positive at any titer. The starting dilution was 1:16 (the test is run in fourfold dilutions; a 2-tube rise in titer is considered significant).

In the double-sandwich IgM ELISA (14), a result of ≥2.0 was interpreted as positive, a result of 1.7 to 1.9 was interpreted as equivocal, and a result of ≤1.6 was interpreted as negative. The following titers were considered positive, negative, and equivocal, respectively, in the following tests: IgA ELISA, ≥2.1, ≤1.4, and 1.5 to 2.0; IgE ELISA, ≥1.9, ≤1.4, and 1.5 to 1.8; IgE ISAGA, ≥4, ≤2, and 3). The AC/HS test was interpreted as previously described (2) by comparing titers obtained with formalin-fixed tachyzoites (HS antigen) with those obtained with acetone-fixed tachyzoites (AC antigen) (2). IgG antibodies formed early in infection recognize stage-specific antigens in the AC preparation which are distinct from those formed later in infection.

The current interpretations of results with the TSP at the PAMF-TSL are as follows. Sera that are obtained within the first two trimesters and are positive with the DT, negative with the IgM, IgA, and IgE ELISAs, and reveal a chronic pattern with the AC/HS test are typically found in patients infected prior to gestation (chronic TSP pattern). Pregnant women with these results are told that the incidence of congenital toxoplasmosis in the offspring of chronically infected women has been shown to be extremely rare (approaching zero) unless a woman is immunocompromised. The combination of high titers with the DT, positive IgM, IgA, and IgE ELISAs, and an acute pattern with the AC/HS test is suggestive of a recent infection (acute TSP pattern). Pregnant women with these serological test results are informed that acute infection during gestation cannot be excluded and that their offspring may be at risk for congenital toxoplasmosis.

A positive DT and IgM ELISA but a negative, low-positive, or equivocal result with the tests for IgA and IgE antibodies and an equivocal pattern with the AC/HS test is more difficult to interpret since it suggests infection acquired prior to gestation but does not entirely rule out recent infection (equivocal TSP pattern). In the latter setting, a follow-up serum sample is usually requested and the two sera are run in parallel. If the follow-up sample does not reveal significant changes with any of the TSP test titers, and if the results from any of the tests of the TSP were lower than one would expect in an acute infection, the diagnosis is most likely infection acquired in the distant past. However, in some patients, despite the testing of serial serum samples in parallel, the interpretation of results from the TSP might remain equivocal. For these patients we recommend a conservative approach, i.e., we suggest that the patient be managed similar to those patients for whom serology results suggest an infection acquired during gestation.

In the present study, sera were selected in which at least one test result in the TSP, or the TSP itself, suggested the possibility of a recently acquired infection. This approach enabled us to evaluate the discriminatory power of testing for IgG avidity. The following criteria were used in the selection of the sera: (i) positive or equivocal results with the IgM ELISA or acute or equivocal pattern with the AC/HS test (69 patients) or (ii) results in the TSP suggested the possibility of a recently acquired infection or acute (16 patients) or equivocal (47 patients) TSP pattern. In 24 of the 47 patients with equivocal TSP patterns, follow up samples run in parallel did not reveal a significant rise in serological test titers, suggesting that their infections were acquired in the distant past (prior to conception).

Measurement of toxoplasma IgG avidity was performed and interpreted according to the directions of the manufacturer with a two-step enzyme immunoassay sandwich method with a final fluorescent detection system (VIDAS Toxo-IgG Avidity kit; bioMérieux, Marcy-l'Etoile, France). This test is performed by the fully automated VIDAS machine which also automatically executes the calculation and interpretation of results. Interpretation was as follows: <0.200, low avidity (may be seen in acute primary infection with *T. gondii*); 0.200 to <0.300, borderline avidity (primary infection during the last 6 months is possible); >0.300, high avidity (excludes primary infection within the last 16 weeks). The manufacturer states that, with this method, a high-avidity result in the first 16 weeks of pregnancy enables exclusion of a recently acquired infection during gestation (15). The results obtained with the VIDAS Toxo-IgG avidity kit were compared with those obtained in the IgM ELISA and the TSP.

When available, follow-up serum samples obtained at least 3 weeks apart from the initial serum sample as well as sera obtained prior to the initial serum sample submitted to the PAMF-TSL were used to attempt to resolve discrepant results between individual tests. All such sera were run in parallel in each test.

RESULTS

The sera were from 132 women, all within the first 16 weeks of gestation. Comparisons of the results obtained with the IgM ELISA with those obtained with the VIDAS IgG avidity test are presented in Table 1. Follow-up sera from the two patients with negative IgM ELISAs but low-avidity results are shown in

TABLE 2. TSP of two patients with negative IgM and low-avidity results[a]

Patient no.	Specimen date (mo/day/yr)	DT titer	Result (interpretation) for:				AC titer	HS titer	AC/HS interpretation	bioM avidity result	bioM interpretation
			IgM ELISA	IgA ELISA	IgE ELISA	IgE ISAGA					
21	1/23/98	256	1.5 (N)	0.5 (N)	0.7 (N)	0 (N)	200	<100	A	0.035	L
	2/23/98	128	1.3 (N)	0.4 (N)	1.4 (N)	0 (N)	200	<100	A		
42	3/5/96	2,048	0.7 (N)	0.3 (N)	0 (N)	3 (E)	>1,600	>3,200	A	0.127	L
	4/8/96	3,072	0.7 (N)	0.3 (N)	0 (N)	3 (E)	>1,600	3,200	A		

[a] N, negative; P, positive; E, equivocal; A, acute; L, low; bioM, bioMérieux.

TABLE 3. Comparison of the VIDAS IgG avidity test and TSP results for 132 serum samples from pregnant women during the first 16 weeks of gestation

Avidity result	No. (%) of samples with TSP pattern		
	Acute (n = 16)	Equivocal (n = 47)	Chronic (n = 69)
Low	8 (50)	7 (14.9)	2 (2.9)
Borderline	3 (18.7)	10 (21.3)	5 (7.2)
High	5 (31.3)	30 (63.8)	62 (89.9)

Table 2. Despite the low-avidity results in these two patients, their initial serological test results were typical for infection acquired in the distant past. The lack of a significant rise in the second sample confirmed this interpretation (infection was acquired in the distant past).

Comparisons of the results obtained with the TSP with those obtained with the VIDAS IgG avidity test are presented in Table 3. Follow-up sera from the two patients with chronic TSP but low-avidity results are shown in Table 4. Based on avidity test results alone, these serological test results may erroneously have been interpreted as most likely consistent with a recently acquired infection. Despite the low-avidity results, their overall serological test results were interpreted as most consistent with an infection acquired in the distant past. The lack of a significant rise in titers in the second sample confirmed that the infection was most likely acquired in the distant past.

In 93 (70.5%) of the 132 cases, the original TSP without inclusion of the avidity test was interpreted by physicians in the PAMF-TSL as indicative of an infection acquired prior to conception. In 39 (29.5%) of the 132 cases, the results from the TSP were such that infection acquired during pregnancy or around the time of conception could not be ruled out. In these women, spiramycin had been recommended to attempt to prevent transmission of the parasite from mother to fetus. IgG avidity testing of the 39 sera revealed high avidity in 19 (48.7%) patients, borderline avidity in 8 (20.5%) patients, and low avidity in 12 (30.8%) patients. Among these 39 patients, 16 (41%) had an acute TSP and 23 (59%) had an equivocal TSP. Five (31.3%) of the 16 patients with an acute TSP and 14 (60.9%) of the 23 patients with an equivocal TSP had high-avidity antibodies.

Of the 35 women with low- or borderline-IgG-avidity antibodies, 11 (31.4%) had an acute TSP, 17 (48.6%) had an equivocal TSP, and 7 (20%) had a chronic TSP. Of 97 women with high-avidity antibodies, 5 (5.2%) had a clearly acute TSP, 30 (30.9%) had an equivocal TSP, and 62 (63.9%) had a clearly chronic TSP.

The detection of high-affinity antibodies in 35 of the 63 patients classified as TSP acute or equivocal reduced by 55% the number of patients in this selected sample that would have been managed as having a recently acquired infection.

DISCUSSION

The results described above reveal that, when used as a confirmatory test along with the TSP in women in the first 16 weeks of gestation, the VIDAS IgG avidity kit is a useful addition to the discriminatory power of the TSP in distinguishing recently acquired infection from chronic infection. However, our findings also suggest that avidity test results, namely those that are borderline or low, have the potential to be misinterpreted, particularly in those sera negative for IgM antibodies and/or with a clearly chronic pattern in the TSP; based on the avidity test alone, the results for these sera would have been erroneously interpreted as consistent with a recently acquired infection.

The VIDAS IgG avidity test was useful in sera with equivocal results with the IgM ELISA test or TSP. Equivocal results in either test are often difficult to interpret, and usually a follow-up sample is required. Even then, in some instances uncertainty in the interpretation remains. Equivocal results with the IgM and TSP can also lead to additional, and in some cases unnecessary, interventions (i.e., use of spiramycin or amniocentesis). For some of these patients, at the time of our recommendation for follow-up testing, treatment with spiramycin and amniotic fluid PCR testing are recommended. Seven (87.5%) of 8 women with equivocal results with the IgM ELISA and 30 (63.8%) of 47 women with equivocal results with the TSP had high-IgG-avidity antibodies and therefore were diagnosed as most likely infected prior to conception. Thus, in women with equivocal results with the IgM ELISA or TSP, the presence of high-avidity antibodies tipped the scale and increased the certainty towards the final interpretation as being consistent with infection acquired prior to gestation. This avoided the need for follow-up samples, treatment with spiramycin, and amniocentesis. These results suggest that in women in the first 16 weeks of gestation whose results with the IgM test or TSP are equivocal, a VIDAS IgG avidity test is warranted.

The benefit of demonstrating high-avidity antibodies was also observed in sera that were positive with the IgM ELISA or had an acute pattern with the TSP. A number of women with

TABLE 4. TSP of two patients with chronic TSP and low-avidity results[a]

Patient no.	Specimen date (mo/day/yr)	DT titer	Result interpretation for:				AC titer	HS titer	AC/HS interpretation	bioM avidity result	bioM interpretation
			IgM ELISA	IgA ELISA	IgE ELISA	IgE ISAGA					
21	1/23/98	256	1.5 (N)	0.5 (N)	0.7 (N)	0 (N)	200	<100	A	0.035	L
	2/23/98	128	1.3 (N)	0.4 (N)	1.4 (N)	0 (N)	200	<100	A		
75	5/1/98	128	2.7 (P)	1.8 (E)	0.9 (N)	0 (N)	200	100	A	0.133	L
	5/22/98	512	1.8 (E)	1.6 (E)	0.3 (N)	3 (E)	200	200	A		

[a] N, negative; P, positive; E, equivocal; A, acute; L, low.

a positive IgM ELISA or an acute TSP had high-avidity antibodies, suggesting that the infection was acquired prior to gestation. The apparent discrepancy in these results may be a reflection of the various windows of time at which results of different tests evolve from acute to chronic and that this window might also vary from patient to patient.

In sera with low- or borderline-avidity antibodies and negative IgM antibodies or a chronic TSP, the VIDAS IgG avidity test did not prove useful and, if used alone, was potentially misleading. Forty percent of women negative with the IgM ELISA had borderline- or low-avidity antibodies. Most of them had a TSP consistent with an infection acquired in the distant past. Similarly, 10% of patients with a chronic TSP had borderline- or low-avidity antibodies. In these patients (chronically infected based on the IgM and TSP results), an avidity test result, if used alone, would have been misinterpreted as suggestive of a recently acquired infection. Low- or borderline-IgG-avidity antibodies are known to persist for months to more than 1 year and, for this reason, are not reliable for the diagnosis of recently acquired infection (1, 3, 5–7, 9, 15, 19). Twenty percent of women with low- or borderline-IgG-avidity antibodies had a chronic TSP; for these patients, a recommendation for the use of spiramycin and amniocentesis would have been unnecessary.

The ultimate goal of toxoplasma serological testing during pregnancy is to establish whether a pregnant woman with IgG antibodies acquired her infection during gestation. The potential pitfalls of relying solely on an IgM test as a discriminatory method to allow such distinction have been reported by our group and by others (11, 12, 21). The TSP represents a step forward and has higher discriminatory power than the IgM tests alone (10). Furthermore, the TSP has been reported to decrease by 50% the rate of unnecessary abortions in women reported to have IgM toxoplasma antibodies (10). Findings in our previous study, using the Labsystems avidity method (9), and those in the present study suggest that avidity testing enhances the efficacy of the TSP in establishing whether a woman has been infected during gestation.

At the present time, our data suggest that although the avidity test represents an additional confirmatory method (most useful if high-avidity antibodies are detected), it should not be used as the only confirmatory test for pregnant women with IgG and/or IgM antibodies because of the potential to misinterpret low- or borderline-avidity antibody results. Confirmatory testing, with the TSP and the VIDAS avidity method, in pregnant women during the first 16 weeks of gestation has the potential to decrease the need for follow-up sera and thereby reduce costs, to make the need for PCR on amniotic fluid and for treatment of the mother with spiramycin unnecessary, to remove the pregnant woman's anxiety associated with further testing, and to decrease unnecessary abortions (9).

The interpretation of avidity test methods has previously been based solely on results in sera obtained sequentially from pregnant women in whom seroconversion had occurred and not on the outcome in their offspring. Follow-up data in only a small number of children (13 children) who were born to mothers who had high-avidity antibodies in the first trimester have been published (8). None were found to be infected with *T. gondii* upon long-term serological follow-up (8). Lack of follow-up data in the offspring is not unique to avidity testing. Follow-up data in the offspring is difficult to obtain, particularly if the result of the serological test obtained during pregnancy was consistent with an infection acquired in the distant past. It is of paramount importance for such data to be collected and evaluated before the specificity of avidity tests can be known.

At present, commercial avidity tests have not been released for marketing in the United States. The PAMF-TSL routinely employs the avidity test as an additional confirmatory diagnostic method in the TSP for those patients with a positive and/or equivocal IgM test or acute and/or equivocal TSP. Health care providers involved in the care of pregnant women should be aware that avidity testing is only a confirmatory test. It should not be used alone as a definitive test for decision making.

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