The Clinical Utility of Measuring Complement and Anti-dsDNA Antibodies During Pregnancy in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** The importance of low complement and anti-dsDNA during pregnancy in patients with systemic lupus erythematosus (SLE) is poorly defined. We investigated the effect of these laboratory tests and clinical SLE activity on pregnancy outcomes.

Methods. We conducted a study of all pregnancies in patients with SLE followed from 1986 to 2002 in a cohort of patients with SLE. At each visit, the physician's estimate of activity (PEA), complement, and anti-dsDNA antibody were measured. We assessed the combination of moderate to severe SLE clinical activity (defined as PEA ≥ 2) and these serologic measurements on pregnancy outcomes. Pregnancies electively terminated were excluded from our study.

Results. Regardless of SLE activity, low complement or positive anti-dsDNA in the second trimester was associated with a higher rate of pregnancy loss and preterm birth. Patients with the combination of either high clinical activity of SLE and low complement or positive anti-dsDNA had the highest rate of pregnancy loss and preterm birth.

Conclusion. Women with the combination of high clinical activity with serologic markers of SLE activity are at highest risk for pregnancy loss and preterm delivery. While hypocomplementemia and positive anti-dsDNA alone are predictive of poor pregnancy outcomes in the second trimester, the risks are far higher for the women in whom this is coupled with clinically active SLE. (J Rheumatol First Release March 15 2011; doi:10.3899/jrheum.100746)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCY dsDNA ANTIBODY
COMPLEMENT PRETERM BIRTH

Systemic lupus erythematosus (SLE) occurs primarily in women of reproductive age. Pregnancy outcomes for these patients have been shown to be largely dependent on SLE activity just prior to and during pregnancy. Several studies have also shown that a decreased level of C3 is associated with pregnancy loss or intrauterine growth retardation[1,2]. The effect of C4 and anti-dsDNA is less clear. We have analyzed a large cohort of pregnancies during SLE to find an association among abnormal serologic measurements, clinical disease activity, and pregnancy outcomes.

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The Hopkins Lupus Cohort and Lupus Pregnancy Center are supported by NIAMS RO1 AR43737 and the Hopkins General Clinical Research Center MOIRR00052. Dr. Clowse is supported by the Arthritis Foundation.

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Accepted for publication January 5, 2011.

MATERIALS AND METHODS

The Hopkins SLE Cohort enrolled consecutive patients with SLE between 1986 and 2002 seen by 1 rheumatologist. This cohort was approved by the Johns Hopkins Institutional Review Board and all patients signed informed consent prior to enrollment. The pregnant patients with SLE were seen every 4–6 weeks during pregnancy. Laboratory tests, including complement levels C3 and C4 and anti-dsDNA antibody (by Crithidia), were obtained at each clinic visit. The physician recorded the physician's estimate of activity (PEA) at each visit as well. Disease control was obtained through the use of hydroxychloroquine, prednisone, and azathioprine as needed.

The PEA is a validated visual analog scale to measure SLE activity based on symptoms and signs[3]. The score is measured as 0–3 (0, no SLE activity; 1, mild activity; 2, moderate activity; and 3, severe activity). The PEA was determined by the clinician at the time of the office visit and did not take into account the current complement or anti-dsDNA titer. For the analysis in our study, we divided the pregnancies by maximum PEA during each trimester. A PEA of 2 or higher was considered an indication of highly active SLE.

Hypocomplementemia was defined by the normal laboratory values at the time the level was drawn. Women with a known complement deficiency were excluded from this analysis. Anti-dsDNA was considered positive if it was ever elevated during pregnancy, regardless of titer. Antiphospholipid syndrome was defined according to the Sapporo criteria[4].

Obstetrical outcomes. Fetal loss included all pregnancies that did not end with a live birth. A preterm delivery was counted as any live birth that occurred before 37 weeks of gestation. "Small for gestational age" included infants that weighed under the 10th percentile for gestational age at delivery. Two infants were excluded from this portion of the analysis because their birth weight was not known.

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Elective terminations are defined in our study as abortions performed for social reasons. Pregnancies that ended in elective termination were not included in the data presented in our study.

Statistical analysis. Some women entered the cohort late in pregnancy and therefore were not at risk for early pregnancy outcomes. For that reason, we analyzed the data by trimester, including in each trimester analysis only those women at risk for a subsequent event and for whom complement, anti-dsDNA, and activity data were available. A woman was included in the low complement or anti-dsDNA group only during the trimesters in which this laboratory finding was identified. For example, a woman would be included in the low complement group in the first trimester but not the second or third if her complement was low in the first but normalized in the second and third trimesters. Given that some women in the cohort had several pregnancies, a generalized estimating equation model was used to account for the lack of independence between these pregnancies in calculating p values[5]. P values were calculated to compare all groups of pregnancies by trimester, to compare pregnancies with low and high clinical activity by trimester, and to compare pregnancies with normal or abnormal laboratory findings.

RESULTS

The cohort included 267 pregnancies in 203 women with SLE. Complement values were available for 263 pregnancies and anti-dsDNA for 264 pregnancies. The demographics were similar to those included in prior reports of this cohort: 60% white, 37% African American; mean maternal age was 29.7 ± 5.4 years; and the mean duration of SLE prior to pregnancy was 5.5 ± 4.8 years.

Low complement and positive anti-dsDNA were associated with several measures of increased SLE activity. More women with hypocomplementemia in pregnancy had a history of renal involvement or an SLE-related rash during pregnancy. Low complement did not appear to correlate, however, with the presence or degree of proteinuria during pregnancy, nor the presence of inflammatory arthritis. A positive anti-dsDNA in pregnancy was associated with proteinuria over 500 mg/24 h and arthritis, but not rash. Women with low complement or positive anti-dsDNA during pregnancy were more likely to receive prednisone, particularly at a dose over 20 mg, than women with normal complement or negative anti-dsDNA. There was a higher rate of hydroxychloroquine discontinuation at the time of pregnancy in women with a positive anti-dsDNA. Discontinuation did not appear to affect complement in pregnancy. Azathioprine use was higher, but not statistically significant, for women with low complement or positive anti-dsDNA.

Low complement (C3 and/or C4) occurred at some point in 136 (52%) of the pregnancies (Table 1). Low C3 alone was found in 20 pregnancies, low C4 alone in 35 pregnancies, and both low C3 and C4 in 81 pregnancies. Pregnancy outcomes within these variations of low complement were not statistically different. Risk factors for poor pregnancy outcomes, including older maternal age, African American race, and antiphospholipid syndrome were not different between women with normal and low complement (Table 1). High clinical activity SLE occurred in 24% of women with low complement compared to 20% with normal complement (not a statistically significant difference). Of women with low clinical SLE activity, 45% had low complement in the first trimester and 39% in the second and third trimesters.

Table 1. Characteristics of the pregnancies in the study by serologic findings throughout pregnancy.

Characteristics	Normal Complement (%)	Low Complement (%)	Negative Anti-dsDNA (%)	Positive Anti-dsDNA (%)
No. pregnancies	127 (48)	136 (52)	150 (57)	114 (43)
Ethnicity				
White	78 (61)	79 (58)	99 (66)	59 (52)
African American	47 (37)	50 (37)	47 (31)	50 (44)
Maternal age, yrs, mean (SD)	29.5 (5.5)	29.9 (5.3)	30.0 (5.5)	29.3 (5.2)
High SLE clinical activity in pregnancy (PEA ≥ 2)	26 (20)	32 (24)	26 (17)	32 (28)*
History of renal disease by ACR criteria	41 (32)	65 (48)*	53 (35)	54 (47)
Proteinuria (> 500 mg/24 h) during pregnancy	26 (21)	42 (31)	25 (17)	43 (38)**
Maximum proteinuria during pregnancy	3.8 g ± 4.4 g	3.5 g ± 5.0 g	2.3 g ± 2.6 g	4.2 g ± 5.5 g
SLE rash in pregnancy	23 (18)	45 (33)*	37 (25)	32 (28)
SLE arthritis in pregnancy	22 (17)	31 (23)	22 (15)	31 (27)*
Any prednisone use in pregnancy	74 (58)	107 (79)*	87 (58)	95 (83)**
Prednisone dose > 20 mg in pregnancy	29 (23)	59 (43)*	36 (24)	52 (46)*
HCQ use				
No HCQ in pregnancy	84 (66)	90 (66)	106 (71)	69 (61)
HCQ all pregnancy	28 (22)	27 (20)	31 (21)	24 (21)
Stopped HCQ for pregnancy	12 (10)	16 (12)	11 (7)	17 (15)*
Azathioprine use in pregnancy	10 (8)	20 (15)	12 (8)	19 (17)
Antiphospholipid syndrome	10 (8)	16 (12)	10 (7)	16 (14)
Low complement	—	—	48 (32)	88 (77)**
Positive anti-dsDNA	26 (20)	88 (65)**	—	—

* $p < 0.05$, ** $p < 0.0001$. SLE: systemic lupus erythematosus; PEA: physician's estimate of activity; ACR: American College of Rheumatology; HCQ: hydroxychloroquine.

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A positive titer of anti-dsDNA was found at some point in 114 (43%) of the pregnancies (Table 1). There was overlap between the pregnancies with low complement and those with positive anti-dsDNA: 101 (38%) had negative anti-dsDNA and normal complement throughout pregnancy, 88 (33%) had positive anti-dsDNA and low complement, 26 (10%) had positive anti-dsDNA and normal complement, and 48 (18%) had negative anti-dsDNA and low complement. A higher rate of increased clinical SLE activity was found in pregnancies with positive anti-dsDNA. Of women with low clinical SLE activity, 40% had positive anti-dsDNA in the first trimester, 32% in the second trimester, and 34% in the third trimester.

We have shown that a high level of SLE activity leads to a significant increase in perinatal mortality and preterm birth, with a decrease in live birth rates and full-term deliveries[6]. While more women with clinically active SLE and low complement in the first trimester had a fetal loss or preterm birth, this difference was not statistically significant, possibly because of the small number of pregnancies with active clinical SLE (Table 2). The rate of fetal loss was significantly higher in the second trimester among women with high-activity SLE, low complement, and the combination of these risk factors. Preterm delivery was higher for women with increased SLE activity in the second trimester, but especially for women with both increased activity and hypocomplementemia. While the rate of preterm births for women with both low complement and high clinical SLE activity in the third trimester was higher than in the other groups, this difference was not statistically significant. Low birth weight, defined as small for gestational age, was not significantly associated with SLE activity and/or complement in any trimester.

The presence of anti-dsDNA is not an indication of increased clinical SLE activity: many patients will have anti-dsDNA, but no clinically apparent disease activity[7]. This was demonstrated in this cohort: 72% of women with anti-dsDNA did not have high clinically active SLE. However, more women with anti-dsDNA had high clinical SLE activity (28%) compared to those with low clinical activity (17%; $p < 0.05$). In this population of pregnant patients, the presence of anti-dsDNA in the second trimester was associated with a higher rate of pregnancy loss ($p = 0.039$) and preterm birth ($p = 0.032$; Table 3). The combination of active clinical SLE and anti-dsDNA during the second trimester was associated with a higher rate of preterm birth, but the association with pregnancy loss was not statistically significant. The combination of high clinically active SLE and anti-dsDNA in the third trimester did not appear to increase the risk for poor pregnancy outcomes. Low birth weight was not associated with anti-dsDNA in any trimester.

DISCUSSION

The clinical utility of measuring complement and anti-dsDNA antibodies is highest among pregnant women with high clinically active SLE. Among women with clinically inactive SLE in pregnancy, the presence of low complement has little effect on pregnancy outcomes. Hypocomplementemia or a positive anti-dsDNA in the second trimester, however, is associated with a higher rate of

Table 2. Pregnancy outcomes by SLE clinical disease activity and complement based on measurements made during each trimester. Only women observed during the trimester of pregnancy under study were included in each group.

	Low-activity SLE		High-activity SLE				
	Normal C3/C4 (%)	Low C3/C4 (%)	Normal C3/C4 (%)	Low C3/C4 (%)	Compares All 4 Groups	p Compares Low and High Activity	Compares Low and Normal Complement
First trimester							
N	84	68	4	8			
Fetal loss	12 (14)	10 (15)	1 (25)	4 (50)	0.57	0.05	0.55
Preterm*	25 (35)	27 (47)	1 (33)	3 (75)	Too few**	Too few**	0.11
SGA†	13 (18)	7 (12)	1 (33)	2 (50)	Too few**	Too few**	0.50
Second trimester							
N	118	76	13	16			
Fetal loss	7 (6)	7 (9)	0 (0)	6 (38)	0.05	0.019	0.021
Preterm*	36 (32)	26 (38)	9 (69)	9 (90)	0.004	0.0003	0.27
SGA†	25 (23)	12 (17)	8 (23)	1 (10)	0.59	0.71	0.31
Third trimester							
N	112	71	17	13			
Fetal loss	0	1 (1)	2 (12)	1 (8)	Too few**	Too few**	Too few**
Preterm*	39 (35)	27 (39)	7 (47)	8 (67)	0.24	0.059	0.35
SGA†	27 (25)	12 (17)	5 (35)	3 (25)	0.55	0.36	0.26

* Percentages are of live births that were preterm (delivered prior to 37 weeks gestation). ** Too few fetal losses to allow statistical analysis. † Small for gestational age: birth weight < 10th percentile for gestational age. SLE: systemic lupus erythematosus.

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Table 3. Pregnancy outcomes by SLE clinical disease activity and presence of the anti-dsDNA antibody, based on measurements made at each trimester. Only women observed during the trimester of pregnancy under study were included in each group.

	Low-activity SLE		High-activity SLE		p		
	Anti-dsDNA Absent (%)	Anti-dsDNA Present (%)	Anti-dsDNA Absent (%)	Anti-dsDNA Present (%)	Compares All 4 Groups	Compares Low and High Activity	Compares with/without Anti-dsDNA
First trimester							
N	92	61	3	9			
Fetal loss	12 (13)	10 (16)	1 (33)	4 (44)	0.46	0.049	0.29
Preterm*	30 (38)	22 (43)	0	4 (80)	Too few**	Too few**	0.27
SGA†	12 (15)	8 (16)	1 (50)	2 (40)	Too few**	Too few**	0.77
Second trimester							
N	131	63	13	16			
Fetal loss	6 (5)	8 (13)	3 (23)	3 (19)	0.11	0.019	0.039
Preterm*	39 (31)	23 (42)	7 (70)	11 (85)	0.0029	0.0003	0.032
SGA†	25 (20)	12 (22)	2 (20)	2 (15)	0.96	0.71	0.94
Third trimester							
N	121	62	21	9			
Fetal loss	1 (1)	0 (0)	3 (14)	0 (0)	Too few**	Too few**	Too few**
Preterm*	40 (33)	26 (42)	11 (61)	4 (44)	0.17	0.061	0.45
SGA†	24 (20)	15 (24)	8 (44)	0 (0)	0.18	0.36	0.69

* Percentages are of live births that were preterm (delivered prior to 37 weeks gestation). ** Too few events to allow statistical analysis. † Small for gestational age: birth weight < 10th percentile for gestational age. SLE: systemic lupus erythematosus.

poor pregnancy outcomes. The women with both highly active SLE and these serologic markers had a far higher rate of poor pregnancy outcomes than women with the serologic marker alone. We suspect that we could not find a statistical difference during early pregnancy because there were too few women who had increased clinical SLE activity in the first trimester.

Prior reports by our group using the same cohort have shown the damaging effect of uncontrolled SLE clinical activity on pregnancy. First trimester activity, whether measured using the PEA, proteinuria, or thrombocytopenia, is associated with a 40% pregnancy loss rate[8]. Increased SLE clinical activity in the latter half of pregnancy is more highly associated with preterm birth, with two-thirds of women delivering early following highly clinically active SLE[6].

Hypocomplementemia is a common finding in patients with SLE. In some cases, it can be associated with increased SLE activity, presumably through the rapid consumption of complement at the location of inflammation[7,9]. During pregnancy, complement may increase by 10%–50% because of increased synthesis of these proteins in the liver[10]. For this reason, interpretation of complement can be challenging in pregnancy. We were surprised to find that, despite this expected rise, 52% of patients in this cohort had a low level of complement at some point during pregnancy.

Complement activation at the level of the placenta has been implicated in fetal demise in a model of antiphospholipid syndrome[11]. Following the infusion of antiphospholipid antibodies, pregnant mice suffer a high rate of pregnancy loss, with pathologic analysis showing both antibody and complement deposition. Several small studies of placentas from women with SLE have identified complement deposition[12]. The significance of this finding, however, is unclear. In normal human placentas, immunoglobulins and complement can be found in a linear pattern along the trophoblast basement membrane, in the intravillous space, and along vessel walls[12]. A study comparing 12 placentas from women with SLE to 7 from women with diabetes and 10 healthy controls found complement (C3) deposition in 2 with SLE, 2 with diabetes, and 5 controls. Both patients with SLE had normal complement during pregnancy and both had live births (although 1 infant had congenital heart block)[13]. Another report of 5 SLE placentas found 1 placenta with a granular pattern of IgG and C3 deposition on the trophoblast basement membrane, in a pattern reminiscent of the pathologic findings in SLE nephritis. This mother had active SLE nephritis at the time of delivery, with low complement and high anti-dsDNA levels[14]. Another study found similar granular deposits of C3 on the trophoblastic basement membrane in 2 out of 11 placentas from women with SLE[15]. These studies are not sufficient to determine whether the consumption of complement associated with active SLE may occur, to some extent, on the placenta. It is also possible that the presence of hypocomplementemia is simply a biomarker for more aggressive SLE, which is associated with a higher rate of pregnancy complications.

Anti-dsDNA is highly specific for SLE and has been

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associated with SLE nephritis. These antibodies form immune complexes that deposit in the glomerulus, promoting inflammation and the ensuing nephritis. The effect of anti-dsDNA on the placenta is not well studied. The same placenta from the woman with active SLE nephritis that had granular C3 deposits also contained IgG that was eluted with deoxyribonuclease, implying that these were anti-dsDNA[14]. It seems more likely that the presence of the anti-dsDNA is a marker of more highly active SLE than a primary cause of placental pathology.

Hypocomplementemia and anti-dsDNA are most helpful in determining pregnancy risks in a woman with highly clinically active SLE. Low complement and/or a positive anti-dsDNA were found in up to 45% of women with low clinical SLE activity, and in these patients, do not demand specific intervention. While either marker alone in the second trimester is indicative of pregnancy risk, when found in a woman with highly clinically active SLE, they are a cause for alarm.

REFERENCES

1. Cortes-Hernandez J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology 2002;41:643-50.
2. Devoe LD, Loy GL. Serum complement levels and perinatal outcome in pregnancies complicated by systemic lupus erythematosus. Obstet Gynecol 1984;63:796-800.
3. Petri M. Hopkins Lupus Pregnancy Center: 1987 to 1996. Rheum Dis Clin North Am 1997;23:1-13.
4. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309-11.
5. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.
6. Clowse ME, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005; 52:514-21.
7. Gladman DD, Urowitz MB, Keystone EC. Serologically active clinically quiescent systemic lupus erythematosus: a discordance between clinical and serologic features. Am J Med 1979;66:210-5.
8. Clowse ME, Magder LS, Witter F, Petri M. Early risk factors for pregnancy loss in lupus. Obstet Gynecol 2006;107:293-9.
9. Ho A, Barr SG, Magder LS, Petri M. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum 2001; 44:2350-7.
10. Buyon JP, Cronstein BN, Morris M, Tanner M, Weissmann G. Serum complement values (C3 and C4) to differentiate between systemic lupus activity and pre-eclampsia. Am J Med 1986; 81:194-200.
11. Salmon JE, Girardi G. Antiphospholipid antibodies and pregnancy loss: a disorder of inflammation. J Reprod Immunol 2008;77:51-6.
12. Ackerman J, Gonzalez EF, Gilbert-Barness E. Immunological studies of the placenta in maternal connective tissue disease. Pediatr Dev Pathol 1999;2:19-24.
13. Hanly JG, Gladman DD, Rose TH, Laskin CA, Urowitz MB. Lupus pregnancy. A prospective study of placental changes. Arthritis Rheum 1988;31:358-66.
14. Grennan DM, McCormick JN, Wojtacha D, Carty M, Behan W. Immunological studies of the placenta in systemic lupus erythematosus. Ann Rheum Dis 1978;37:129-34.
15. Abramowsky CR. Lupus erythematosus, the placenta, and pregnancy: a natural experiment in immunologically mediated reproductive failure. Prog Clin Biol Res 1981;70:309-20.

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