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Pregnancy outcomes among African–American patients with systemic lupus erythematosus compared with controls

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ABSTRACT

Objective: In a study of Gullah African–Americans, we compared pregnancy outcomes before and after systemic lupus erythematosus (SLE) diagnosis to controls to test whether there is a predisease state that negativelyaffects pregnancy outcomes.

Design: Cases and controls reporting at least one pregnancy were included. Controls were all Gullah African-American females. We collected demographic, socioeconomic and pregnancy data. We modelled pregnancy outcome associations with case status using multiple logistic regression to calculate ORs.

Results: After adjustment for age, years of education, medical coverage and pregnancy number, compared with controls, cases were more likely to have any adverse outcome (OR 2.35, 95% CI 1.78 to 3.10), including stillbirth (OR 4.55, 95% CI 1.53 to 13.50), spontaneous abortion (OR 2.05, 95% CI 1.40 to 3.00), preterm birth (OR 2.58, 95% CI 1.58 to 4.20), low birth weight (OR 2.64, 95% CI 1.61 to 4.34) and preeclampsia (OR 1.80, 95% CI 1.08 to 3.01). The odds of adverse pregnancy outcomes all increased after SLE diagnosis compared with before diagnosis, even after adjustment for age, years of education, pregnancy number and medical coverage.

Conclusion: From a large cohort of African–American women, our findings suggest there may be a predisease state that predisposes to adverse pregnancy outcomes.

KEY MESSAGES

- Among a unique African American cohort, there is an increased risk of adverse pregnancy outcomes in SLE cases both before and after SLE diagnosis compared with controls.
- There may be a predisease state in SLE that negatively impacts pregnancy outcomes and may not be entirely antibody mediated.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a strong female predominance. African-Americans have a threefold increased prevalence of SLE, develop SLE at an earlier age and have increased SLE-related morbidity and mortality compared with Caucasians.[1–5] SLE diagnosis is associated with adverse pregnancy outcomes with an increased risk of preeclampsia, preterm live birth, low birth weight, spontaneous abortion (SAB) and stillbirth.[6–14] However, the question of whether there is a difference between outcome risk before versus after diagnosis of SLE has not been well studied in an African-American cohort. Previous studies have examined adverse pregnancy outcomes with respect to timing of disease onset, but only a few of those studies used a control group.[6 7 9] These studies were limited by low number of pregnancies after SLE diagnosis,[7 9] and only one investigated rates of preeclampsia before and after SLE diagnosis.[6]

Using data from a large, well-characterised case–control study of Gullah African-Americans, we compared pregnancy outcomes before and after SLE diagnosis to healthy controls. Our study population consisted of an African-American Gullah population of the Sea Islands of South Carolina with a proven homogeneous genetic and environmental background,[15 16] a high prevalence of multipatient families with SLE,[17] and a distinct cultural identity.[18] By examining pregnancy outcomes before and after SLE diagnosis, this study was conducted to explore whether there is a predisease state that negatively affects pregnancy outcomes.

PATIENTS AND METHODS

This research was carried out in compliance with the Helsinki Declaration with the approval of the Institutional Review Board at the Medical University of South Carolina. Data for this study were analysed retrospectively from information collected from study

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visits that were part of a longitudinal observational cohort called SLE in Gullah Health (SLEIGH), which was started in 2002. A more complete description of the cohort has been previously reported.[17] Briefly, eligible cases were (1) age 2 years and above, (2) self-identified as African-American 'Gullah' from the Sea Island region of South Carolina, (3) diagnosed with SLE by meeting at least 4 of the 11 classification criteria as designated by the American College of Rheumatology (ACR),[19 20] (4) able to speak and understand English and (5) able and willing to give informed consent. SLE cases were asked to bring family members and friends from the Gullah community, who were unaffected by SLE, to a study visit for recruitment as potential controls. Controls included in this study were confirmed not to have SLE using a screening interview, examination and laboratory testing.[17] Classification as Gullah required that the subjects self-identify and confirm that parents and grandparents were of Gullah heritage with no known ancestors that were not of Gullah lineage.

Of the 888 participants in the SLEIGH cohort, analyses were restricted to African-American Gullah female cases and controls reporting at least one pregnancy. Demographic, socioeconomic and pregnancy data were collected. Pregnancy outcomes were self-reported with adverse events confirmed by chart review. Stillbirth was defined as pregnancy loss at or after 22 weeks, and SAB as loss before 22 weeks. At the time of study design, the WHO and International Classification of Disease defined stillbirth as greater than 22 weeks.[21] Low birth weight was defined as less than 5 pounds, 8 ounces and preterm live birth as delivery before 37 weeks. Preeclampsia was self-reported based on questions asked by a physician and included "Did you experience high blood pressure during this pregnancy?" If the subject answered yes, then the subsequent question asked was "did your doctor diagnose you with preeclampsia or eclampsia, requiring hospitalisation and treatment, usually delivery of the baby?" If the subject answered yes or was not sure of the answer, a chart review was performed. Preeclampsia was not further classified as mild or severe for this study. Stillbirth and SAB were grouped as fetal loss for secondary analyses. Stillbirth, SAB, low birth weight, preterm live birth and preeclampsia were grouped as any adverse pregnancy outcome for secondary analyses. Medical coverage was defined as receiving healthcare reimbursements from private insurance, Medicaid, Medicare or military benefits. Disability was defined as currently receiving disability payments. Cumulative damage was measured using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI).[22] SDI was considered a dichotomous variable, no damage versus any damage.

Antibody serologies including double-stranded DNA (ds-DNA), SSA, SSB, anticardiolipin antibody (aCL), antibody to β_2-glycoprotein I (anti-β_2GPI) and lupus anticoagulant (LAC) were examined. Baseline measures of SSA, SSB and aCL were done with methods for antibody determination previously described.[17] ds-DNA, anti-β_2GPI and LAC were done at a local laboratory at the Medical University of South Carolina. Anti-β_2GPI and ds-DNA was tested using enzyme linked immunoassay. LAC was tested using a dilute Russell's viper venom time with confirmatory studies. aCL and anti-β_2GPI were considered high-titre positive if IgG or IgM titres were ≥40 units and low-titre positive if IgG or IgM titres were ≥20 units and <40 units.

Categorical variables were examined by χ^2 tests. Differences in the means of continuous variables were compared using Student t test. Pregnancy outcome associations were modelled with case status using multiple logistic regression to calculate ORs and 95% CIs. Covariates included age, years of education, medical coverage, age at the time of pregnancy and pregnancy number. Pregnancy number was defined as order of the pregnancy, not total number of pregnancies. For example, the third pregnancy in a woman with five pregnancies would be coded as three. Elective abortion, preterm birth, low birth weight and preeclampsia were each modelled as separate outcomes. All analyses were conducted using SAS V.9.1 (SAS Institute, Cary, North Carolina, USA). Two-sided p values ≤0.05 were considered significant.

Table 1 Characteristics of African–American Gullah female SLE cases compared with related controls

Characteristics	SLE cases (n=220)	Controls (n=217)	p Value*
Mean age (years)±SD	48.1±12.4	54.3±13.4	<0.01
Mean age (years) at first pregnancy±SD	22.1±5.0	22.1±5.8	0.95
Mean years of education±SD	12.1±1.9	12.1±2.1	0.96
Medical coverage† (%)	82.7	86.6	0.26
Disability‡ (%)	38.6	6.9	<0.01
Employment (%)	32.3	71.9	<0.01
Pregnancies±SD	2.6±1.4	3.2±2.1	<0.01
Live births±SD	2.3±1.2	2.8±1.9	<0.01

*χ^2/t test.
†Includes private insurance, Medicare, Medicaid and military benefits.
‡Currently receiving disability payments.
SLE, systemic lupus erythematosus.

RESULTS

Characteristics of cases (n=220) and controls (n=217) are compared in table 1. Compared with controls, cases were significantly younger (48.1 vs 54.3, p<0.01) at time of data analysis with similar mean years of education (12.1 vs 12.1, p=0.96). Cases had similar medical coverage compared with controls (82% vs 87%, p=0.26), but were significantly more likely to be unemployed (68% vs 28%, p<0.01) and to receive disability payments at time of study enrolment (39% vs 7%, p<0.01). Mean age at first pregnancy was similar in cases versus controls (22 vs 22, p=0.95), and 58% of pregnancies in cases occurred before diagnosis. Compared with controls, cases had significantly fewer pregnancies (2.6 vs 3.2, p<0.01) and live births (2.3 vs 2.8, p<0.01). Cases had fewer pregnancies after SLE diagnosis compared with before (0.7 vs 1.5, p<0.01). Cases had fewer live births after SLE diagnosis compared with before (0.4 vs 1.2, p<0.01). Mean age at SLE diagnosis was 33.0±11.7 years. Mean duration of disease at time of analysis was 14.5±8.4 years. Cases fulfilled a mean of 6.1±1.9 ACR criteria (table 2). Cases had a mean SDI of 2.3±1.9, with 82% having any damage.

Pregnancy outcomes in cases before and after SLE diagnosis compared with controls are detailed in table 3. Of the pregnancies in the control group, 19.1% resulted in adverse outcomes compared with 34.4% before SLE diagnosis and 51.7% after SLE diagnosis. Where the date of diagnosis or pregnancy was unknown, 39.8% of these pregnancies resulted in adverse outcomes. After adjustment for age, years of education, medical coverage and pregnancy number, compared with controls, cases were more likely to have any adverse outcome (OR 2.35, 95% CI 1.78 to 3.10), including stillbirth (OR 4.55, 95% CI 1.53 to 13.50), SAB (OR 2.05, 95% CI 1.40 to 3.00), preterm birth (OR 2.58, 95% CI 1.58 to 4.20), low birth weight (OR 2.64, 95% CI 1.61 to 4.34) and preeclampsia (OR 1.80, 95% CI 1.08 to 3.01). Cases and controls had similar rates of elective abortion.

Table 2 ACR criteria of African-American Gullah female SLE cases

ACR criterion	% cases (n=220)
Malar rash	51.7
Discoid rash	33.5
Photosensitivity	56.7
Oral/nasal ulcers	43.2
Arthritis	86.4
Serositis	42.6
Renal disorder	50.3
Neurologic disorder	18.2
Hematologic disorder	59.8
Immunologic disorder	78.0
Antinuclear antibody positivity	98.1

ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.

Table 3 ORs and 95% CIs for adverse pregnancy outcomes occurring before and after SLE diagnosis compared with controls in an African-American population

	Stillbirth	Spontaneous abortion	Elective abortion	Preterm live birth	Low birth weight	Preeclampsia
Controls	n=5	n=64	n=21	n=29	n=28	n=29
(694 pregnancies)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cases	n=16	n=102	n=22	n=66	n=58	n=45
(all)	4.43	2.20	1.20	2.45	2.62	1.70
(577 pregnancies)	(1.61 to 12.17)*†	(1.58 to 3.08)*	(0.63 to 2.29)†	(1.43 to 4.17)*	(1.52 to 4.52)*	(0.98 to 2.94)
Cases	n=9	n=41	n=8	n=30	n=31	n=28
(before diagnosis)	3.90	1.37	0.83	1.87	2.01	1.80
(337 pregnancies)	(1.30 to 11.76)*†	(0.87 to 2.18)	(0.36 to 1.89)†	(1.07 to 3.28)*	(1.14 to 3.54)*	(1.03 to 3.16)*
Cases	n=5	n=39	n=5	n=26	n=22	n=14
(after diagnosis)	6.15	2.79	1.47	4.70	5.48	2.03
(147 pregnancies)	(1.75 to 21.65)*†	(1.61 to 4.81)*	(0.54 to 3.98)†	(2.42 to 9.13)*	(2.81 to 10.69)*	(0.94 to 4.39)
Cases	n=2	n=22	n=9	n=10	n=5	n=3
(unknown order)	4.02	2.96	4.31	4.62	2.39	1.32
(93 pregnancies)	(0.76 to 21.17)†	(1.59 to 5.48)*	(1.89 to 9.82)*†	(2.10 to 10.16)*†	(0.89 to 6.52)†	(0.38 to 4.50)†

All estimates are adjusted for age, years of education, insurance and pregnancy number.
*p<0.05.
†Unadjusted model.
SLE, systemic lupus erythematosus.

Pregnancies before diagnosis were more likely to end in any adverse outcome (OR 2.23, 95% CI 1.66 to 2.99) compared with controls. Those pregnancies occurring after diagnosis (OR 4.55, 95% CI 3.13 to 6.62) and those with an unknown order of occurrence (OR 2.81, 95% CI 1.78 to 4.43) were more strongly associated with any adverse outcome compared with controls. After adjustment for age, years of education, pregnancy number and medical coverage, the odds of SAB (OR 2.50, 95% CI 1.40 to 4.45), preterm birth (OR 2.94, 95% CI 1.51 to 5.74) and low birth weight (OR 2.98, 95% CI 1.54 to 5.80) all increased after SLE diagnosis compared with before diagnosis. Stillbirth (OR 1.34, 95% CI 0.39 to 4.59), elective abortion (OR 1.15, 95% CI 0.32 to 4.15) and preeclampsia (OR 1.11, 95% CI 0.51 to 2.44) did not increase after SLE diagnosis compared with before diagnosis.

In univariate models, age at first birth (OR 1.07, 95% CI 1.01 to 1.14, p=0.03), age at the time of pregnancy (OR 1.05, 95% CI 1.02 to 1.08, p<0.01), years of education (OR 1.14, 95% CI 1.05 to 1.23, p<0.01), currently working (OR 0.71, 95% CI 0.52 to 0.98, p=0.03) and disability (OR 1.48, 95% CI 1.03 to 2.11, p=0.03) were all associated with fetal loss. In adjusted models, among both cases and controls, age, age at first birth, mean years of education, employment and disability were not associated with fetal loss, elective abortion, preterm birth, low birth weight or preeclampsia.

Using SLE cases with pregnancies after diagnosis, disease duration prior to pregnancy was not associated with fetal loss (OR 1.04, 95% CI 0.94 to 1.14), elective abortion (OR 0.75, 95% CI 0.44 to 1.29), preterm birth (OR 1.07, 95% CI 0.95 to 1.21), low birth weight (OR 1.07, 95% CI 0.95 to 1.21) or preeclampsia (OR 1.05, 95% CI 0.92 to 1.20). Among pregnancies after SLE diagnosis, none of the individual ACR criteria were associated with adverse pregnancy outcomes, nor was SDI associated with fetal loss (OR 2.30, 95% CI 0.67 to 7.90), elective abortion (OR 0.38, 95% CI 0.05 to 3.02), preterm birth (OR 1.59, 95% CI 0.36 to 7.00), low birth weight (OR 3.92, 95% CI 0.69 to 22.22) or preeclampsia (OR 0.60, 95% CI 0.12 to 2.87).

Rates of antibody positivity in pregnancies with and without adverse outcomes in African-American SLE females are shown in table 4. Pregnancies occurring in mothers positive for SSA were significantly more likely to end in adverse outcomes (37.4% vs 22.8%, p=0.048) as well as for pregnancies occurring in mothers positive for SSB (12.9% vs 7.0%, p=0.02) compared with pregnancies in mothers negative for these antibodies. Pregnancies with mothers having any SLE-related antibody approached significance for association with any adverse pregnancy outcome (75.7% vs 68.7%, p=0.07).

ORs for adverse pregnancy outcomes both before and after SLE diagnosis in SLE cases with antibody positivity are shown in table 5. In unadjusted analyses, ds-DNA positivity was associated with preeclampsia (OR 2.18, 95% CI 1.07 to 4.43) and approached significance for low birth weight (OR 1.70, 95% CI 0.93 to 3.12) but was not associated with other adverse pregnancy outcomes. SSA positivity was significantly associated with premature live births (OR 2.27, 95% CI 1.28 to 4.02), low birth weight (OR 2.12, 95% CI 1.17 to 3.85) and approached significance for any adverse outcome (OR 1.47, 95% CI 1.00 to 2.17). SSB positivity was significantly associated with premature live birth (OR 3.89, 95% CI 1.77 to 8.58), low birth weight (OR 2.91, 95% CI 1.24 to 6.82) and any adverse outcome (OR 1.96, 95% CI 1.09 to 3.53). Having any SLE-related antibody was associated with preeclampsia (OR 4.52, 95% CI 1.58 to 12.91) and approached significance for any adverse outcome (1.43, 95% CI 0.98 to 2.08). aCL positivity was associated with a decreased risk of preeclampsia (OR 0.21, 95% CI 0.05 to 0.89). LAC and anti-β_2GPI were not associated with any adverse pregnancy outcomes. Low numbers of adverse pregnancy outcomes precluded stratifying analyses by pregnancies occurring before and after SLE diagnosis or adjusting for covariates.

Table 4 Rates of antibody positivity in pregnancies with and without adverse outcomes in African-American SLE females

Antibody Positivity	Any adverse pregnancy outcome* % (n)	No adverse pregnancy outcome % (n)	p Value
ds-DNA	59.7 (135)	57.5 (200)	0.59
SSA	37.4 (66)	22.8 (73)	0.048
SSB	12.9 (28)	7.0 (22)	0.02
aCL			0.27
Low titre	7.1 (13)	11.5 (29)	
High titre	8.2 (15)	9.5 (24)	
anti-β_2GPI			0.55
Low titre	6.7 (7)	10.7 (16)	
High titre	3.9 (4)	3.3 (5)	
LAC	16.3 (23)	14.8 (31)	0.69
Any SLE-related antibody	75.7 (171)	68.7 (239)	0.07

*Includes stillbirth, spontaneous abortion, low birth weight, preterm live birth and preeclampsia.
Anti-β_2GPI, antibody to β_2-glycoprotein I; LAC, lupus anticoagulant; SLE, systemic lupus erythematosus.

DISCUSSION

Among a large cohort of African-American women, we observed significantly higher rates of adverse pregnancy outcomes in cases both before and after diagnosis of SLE compared with controls. The risk of adverse pregnancy outcomes further increased after SLE diagnosis. Three prior studies have investigated pregnancy outcomes before and after SLE diagnosis using control groups.[6 7 9] Two of these studies had predominantly African–American patients with SLE and found increased adverse pregnancy outcomes both before and after SLE diagnosis compared with control groups.[6 7] However, one study

Table 5 ORs and 95% CIs for adverse pregnancy outcomes in African-American SLE cases with antibody positivity

Antibody positivity	Stillbirth OR (95% CI)	Spontaneous abortion OR (95% CI)	Elective abortion OR (95% CI)	Premature live birth OR (95% CI)	Low birth weight OR (95% CI)	Preeclampsia OR (95% CI)	Any adverse outcome OR (95% CI)
ds-DNA	n=11 1.54 (0.53 to 4.50) p=0.43	n=53 0.77 (0.50 to 1.19) p=0.24	n=15 1.50 (0.60 to 3.75) p=0.39	n=41 1.16 (0.67 to 1.99) p=0.60	n=40 1.70 (0.93 to 3.12) p=0.09	n=34 2.18 (1.07 to 4.43) p=0.03	n=136 1.11 (0.79 to 1.55) p=0.56
SSA	n=4 0.98 (0.31 to 3.12) p=0.98	n=27 1.14 (0.69 to 1.87) p=0.61	n=6 1.18 (0.45 to 3.12) p=0.74	n=25 2.27 (1.28 to 4.02) p<0.01	n=22 2.12 (1.17 to 3.85) p=0.01	n=15 1.61 (0.82 to 3.15) p=0.17	n=66 1.47 (1.00 to 2.17) p=0.053
SSB	n=1 0.70 (0.09 to 5.41) p=0.73	n=12 1.47 (0.73 to 2.95) p=0.28	n=2 1.16 (0.26 to 5.19) p=0.85	n=12 3.89 (1.77 to 8.58) p<0.01	n=9 2.91 (1.24 to 6.82) p=0.01	n=5 1.49 (0.54 to 4.12) p=0.44	n=28 1.96 (1.09 to 3.53) p=0.02
Lupus anticoagulant	n=3 1.52 (0.41 to 5.71) p=0.53	n=8 0.83 (0.37 to 1.88) p=0.65	n=4 1.60 (0.50 to 5.11) p=0.43	n=9 1.53 (0.66 to 3.51) p=0.32	n=5 0.91 (0.33 to 2.53) p=0.86	n=7 1.39 (0.56 to 3.47) p=0.48	n=23 1.13 (0.63 to 2.03) p=0.69
Anticardiolipin*	n=2 0.69 (0.15 to 3.14) p=0.63	n=18 1.22 (0.68 to 2.21) p=0.51	n=3 0.90 (0.25 to 3.20) p=0.87	n=6 0.52 (0.21 to 1.30) p=0.16	n=4 0.43 (0.15 to 1.26) p=0.12	n=2 0.21 (0.05 to 0.89) p=0.03	n=28 0.69 (0.42 to 1.14) p=0.14
Anti-β_2GPI*	n=2 1.52 (0.31 to 7.56) p=0.61	n=3 0.40 (0.12 to 1.37) p=0.14	n=1 0.61 (0.08 to 4.95) p=0.64	n=3 0.63 (0.18 to 2.24) p=0.47	n=5 1.70 (0.57 to 5.06) p=0.34	n=4 1.53 (0.47 to 4.99) p=0.48	n=11 0.73 (0.33 to 1.58) p=0.42
Any SLE-related antibody	n=14 2.98 (0.67 to 13.31) p=0.15	n=75 1.23 (0.75 to 2.01) p=0.41	n=16 1.14 (0.44 to 2.97) p=0.79	n=49 1.23 (0.68 to 2.24) p=0.50	n=44 1.44 (0.75 to 2.80) p=0.28	n=41 4.52 (1.58 to 12.91) p<0.01	n=172 1.43 (0.98 to 2.08) p=0.07

All estimates are unadjusted.
*Includes both low and high titres.
Anti-β_2GPI, antibody to β_2-glycoprotein I; SLE, systemic lupus erythematosus.

found that risk of pregnancy loss was not significantly different before and after SLE diagnosis, but that risk of therapeutic abortion increased after SLE diagnosis compared with before.[9] Notably, the SLE cases in this one study were predominantly white in contrast to other studies in the literature and our current study.[6–7 9] We found similar rates of pregnancy loss, combining SAB and stillbirth, of 14.8% before SLE diagnosis and 29.9% after SLE diagnosis, while Petri and Allbritton found 19% before SLE and 27% after SLE diagnosis.[6] In addition, rates of preterm pregnancies were similar at 8.9% before and 17.7% after SLE diagnosis compared with 6% before and 24% after SLE diagnosis in Petri and Allbritton.[6]

A limitation in our study is that our cohort was not comprised of incident cases; therefore, many patients were diagnosed with SLE before enrolling into the cohort. As much as possible, physician records were obtained to confirm cases' reports of date of diagnosis. In addition, some cases were truly diagnosed with SLE after their pregnancies. In our cohort, less than 10% of SLE cases were diagnosed after age 50, which is consistent with published rates of late-onset SLE, decreasing the likelihood that there was an over-representation of pregnancies classified as occurring before diagnosis.[23] In addition, with a retrospective design, there was potential for recall bias in subjects reporting pregnancy outcomes. Our study may also under-represent early pregnancy loss as often not reported, and data collection did not include questions assessing for pregnancy loss at less than 10 weeks. For the low birth weight outcome, we used a fixed value to determine low birth weight rather than growth curves to determine size for gestational age. There were only 59 pregnancies classified as both preterm and low birth weight that could potentially have been appropriate for gestational age. Although there is the potential for some misclassification, this group represents <5% of the total number of pregnancies and is unlikely to impact the overall associations observed for low birth weight.

Increased rates of adverse pregnancy outcomes occurring before SLE diagnosis could potentially be related to a predisease state, as autoantibodies are known to predate clinical manifestations of SLE.[24] Some of these autoantibodies, particularly antiphospholipid antibodies, are pathogenic to the placenta potentially contributing to adverse pregnancy outcomes.[25] However, there have been conflicting data regarding the strength of association of LAC and aCL with adverse pregnancy outcomes.[11] Our analyses did not show significant associations between adverse pregnancy outcomes and presence of LAC or anti-β_2GPI. In similar studies to our current analyses, one study found a borderline significance for presence of LAC with pregnancy loss but two other studies did not find significant associations of adverse pregnancy outcomes with presence of aCL or LAC.[6 8 12] One multicentre, prospective observational study that included patients with antiphospholipid antibody syndrome, SLE, or both and normal controls found that LAC is the primary predictor of adverse pregnancy outcomes but not aCL or anti-β_2GPI.[26] In a meta-analysis of patients with SLE, the presence of a positive LAC or aCL was associated with preeclampsia and premature birth.[27] In another meta-analysis that excluded women with autoimmune disease, aCL was significantly associated with severe preeclampsia more so than mild preeclampsia.[28] Our analyses did not find these associations as there were few adverse pregnancy outcomes that occurred after SLE diagnosis in cases with available antibodies. In the absence of serial measurements to determine exact date of seroconversion of antibodies, no inferences regarding etiologic associations of antibodies to pregnancy outcomes can be drawn from these data. Although aCL was protective against preeclampsia in this study, this finding was based on two individuals positive for aCL having preeclampsia and is likely a spurious association.

Prior studies have shown increased adverse pregnancy outcomes associated with SSA and SSB positivity.[29] In our unadjusted analyses, pregnancies occurring in mothers with SSA and SSB positivity were significantly more likely to end in adverse outcomes. SSA and SSB were both associated with premature live birth and low birth weight. However, other studies did not show significant associations between SSA and SSB positivity and adverse pregnancy outcomes.[6 8 12]

There was a significant association of ds-DNA positivity with preeclampsia. This finding has been previously reported with hypotheses that ds-DNA antibodies may be pathogenic to the fetus.[30–32] In addition, prior literature reports that SLE antibodies cluster with specific clinical manifestations.[33 34] ds-DNA has been reported to cluster with renal disease,[33 34] which could explain the association between ds-DNA positivity and increased risk of preeclampsia. In another study, ds-DNA positivity was associated with a higher rate of pregnancy loss and preterm birth in the second trimester and even further increased risk in the setting of high disease activity.[35]

A number of demographic characteristics, such as age at pregnancy, were associated with adverse outcomes in univariate models. However, these became non-significant in adjusted models, likely due to low numbers of adverse events. Other studies in the literature focus on association of race and education with adverse pregnancy outcomes with one study investigating social class.[6 8 9] However, there were no studies looking specifically at employment and disability status, as performed in our analysis. Our analyses showed that current disability and unemployment were both associated with a history of fetal loss.

In our study, there was an increased risk of fetal loss with increasing years of education. Our findings are in contrast with others who observed an inverse association between education and adverse outcomes.[6 8] Specifically, one study observed a significant association between preterm birth and non-high school graduates.[6] Another study found fewer years of education was associated with

adverse pregnancy outcomes, which pooled miscarriages, stillbirths, premature birth and therapeutic abortions.[8] Our results likely differ due to different outcomes used in the analysis and due to low numbers of adverse outcomes limiting the ability to adjust for confounders.

Increased risks of adverse pregnancy outcomes in SLE cases have been consistently observed in multiple cohorts. Identification of factors associated with these risks could lead to improved understanding of the underlying mechanism, but also aid in counselling patients on their pregnancy risk. In our study, there was not an association among mean disease duration and SDI and adverse pregnancy outcomes. Other similar cohort studies did not investigate disease duration or SDI. For renal outcomes, there was no significant association of adverse pregnancy outcomes and ACR renal criterion, although low power limited the ability to detect this association. One similar cohort study found that renal involvement, defined as fulfilling ACR renal criterion or biopsy-proven SLE nephritis, was associated with adverse pregnancy outcomes, a composite of miscarriages, stillbirth, premature birth and therapeutic abortions.[8] A meta-analysis of pregnancy outcomes in SLE nephritis cases showed active SLE nephritis was associated with increased risk of premature birth and history of nephritis was associated with higher rates of preeclampsia.[27]

There was no association between any of the ACR criteria and adverse pregnancy outcomes. One cohort study found a higher number of ACR criteria fulfilled at diagnosis were associated with adverse pregnancy outcomes.[8] Notably, this study used a multiethnic cohort of SLE cases with disease duration 5 years or less.[8] Another study did not observe an association between any specific ACR criterion and adverse pregnancy outcomes.[6] In addition, prior studies have investigated complement levels and their association with pregnancy outcomes with mixed results. While one study did not show a significant association with low serum complement levels and pregnancy loss and preterm birth,[6] two other studies did show that decreased serum levels of C3 were associated with pregnancy loss and intrauterine growth restriction.[11 36] However, it is noted that complement levels may fluctuate in normal pregnancies and may not correlate with disease activity in pregnant patients with SLE.[12 37] In response to these concerns, one study showed that low complement levels, especially in the setting of high SLE activity, were associated with increased fetal loss and preterm delivery in the second trimester.[35] In our study, complement levels were measured at the study visits. However, the majority did not have this information during pregnancies, so we were unable to comment on association of complement levels to pregnancy outcomes.

Strengths of this study included a high sample size for SLE cases, controls and number of pregnancies. Our study included controls that allowed for comparison to other cohorts in the literature. Moreover, our cohort consisted of a unique African-American population with similar genetic and environmental backgrounds. Cases and controls were both drawn from the same unique cohort, which allowed for direct comparisons of pregnancy outcomes with high internal validity.

Our study had a number of limitations. Similar to other studies, there were a low number of adverse outcomes limiting power to address confounding thoroughly. With a retrospective analysis, there were missing dates on comorbid conditions that limited the ability to determine associations with adverse pregnancy outcomes. Although disease activity, as measured by SLE Disease Activity Index (SLEDAI),[38] and medication use were obtained at the study visits, the majority did not have this information before or during pregnancies, so we were unable to comment on the contribution of disease activity and medications to adverse pregnancy outcomes. Further, many of the pregnancies occurred approximately 20–30 years ago with less knowledge in the management of high-risk pregnancies and treatment options for SLE. This may have contributed to slight over-representation of adverse outcomes. Our population was restricted to African-American Gullah females with SLE and controls, and so our results from this specific population may not be generalisable to the broader population.

Among a unique cohort of African-American Gullah females with at least one pregnancy, we observed an increased risk of adverse pregnancy outcomes in SLE cases compared with controls both before and after SLE diagnosis. These increased risks remained after adjusting for age, years of education, insurance status and pregnancy number. These findings agree with prior studies in the literature and argue for the presence of a predisease state that could negatively impact pregnancy outcomes. SSA and SSB positivity were associated with adverse pregnancy outcomes, whereas we did not find this association with LAC or anti-β_2GPI. While autoantibodies have been shown to play a role in the risk of adverse pregnancy outcomes, there remain other important disease factors that are also contributing to this risk. Additional prospective studies are needed to understand and characterise risk and protective factors associated with pregnancy outcomes among patients with SLE to guide counselling and future interventions.

Contributors All authors were involved in drafting the article or revising its content, and all authors approved the final version to be published. AB, LW and DLK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: AB, GG and DLK. Acquisition of data: AKM, GG and DLK. Analysis and interpretation of data: AB, LW and DLK.

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