Preconceptional Cardiovascular Health and Pregnancy Outcomes in Women with Systemic Lupus Erythematosus

Amanda M. Eudy, Anna Maria Siega-Riz, Stephanie M. Engel, Nora Franceschini, Annie Green Howard, Megan E.B. Clowse, and Michelle Petri

ABSTRACT. ***Objective.*** To estimate the effects of preconceptional cardiovascular (CV) health, measured by American Heart Association (AHA) guidelines, on pregnancy outcomes in women with systemic lupus erythematosus (SLE).

Methods. The study included patients in the Hopkins Lupus Pregnancy Cohort. Body mass index (BMI), total cholesterol, and blood pressure (BP) in the most recent clinic visit prior to conception or first trimester were used to determine CV health (ideal, intermediate, or poor health) based on AHA definitions. Outcomes included preterm birth, gestational age at birth, and small for gestational age (SGA). Multivariable linear and logistic regression models with generalized estimating equations estimated the association of each CV health factor and outcome.

Results. The analysis included 309 live births. There were 95 preterm births (31%), and of the 293 pregnancies with birth weights, 18% were SGA. Ideal BMI, total cholesterol, and BP were reported in 56%, 85%, and 51% of pregnancies, respectively. Intermediate BMI was associated with decreased odds of SGA (OR 0.26, 95% CI 0.11–0.63), adjusted for race and prednisone use. Intermediate/poor total cholesterol was associated with increased odds of preterm birth (OR 2.21, 95% CI 1.06–4.62). Intermediate/poor BP was associated with decreased gestational age at birth (β –0.96, 95% CI –1.62 to –0.29).

Conclusion. Poor/intermediate preconception CV health affects pregnancy outcomes of preterm birth and SGA infants among women with SLE. Efforts to maintain BMI, total cholesterol, and BP within the recommended ideal range prior to pregnancy is important to improve pregnancy outcomes in women with SLE. (First Release July 15 2018; J Rheumatol 2019;46:70–7; doi:10.3899/jrheum.171066)

Key Indexing Terms:
BIRTH WEIGHT CARDIOVASCULAR DISEASES PREGNANCY
PREMATURE BIRTH SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease that largely affects women, with disease onset typically occurring between ages 15 and 44[1]. Although pregnancy outcomes in women with SLE have improved, the prevalence of preterm birth and infants born small for gestational age (SGA) remains 2 to 6 times greater in women with SLE compared to the general population[2,3,4]. Well-established risk factors for adverse pregnancy outcomes in the general population, such as body mass index (BMI), cholesterol, physical activity, and diet, have not been investigated in SLE.

The American Heart Association (AHA)'s 2020 Impact Goals included the development of the concept of "ideal cardiovascular health," which focuses on primary prevention and is composed of seven modifiable cardiovascular (CV) metrics: health factors [glucose, total cholesterol, and blood pressure (BP)] and health behaviors (BMI, physical activity, diet, and cigarette smoking)[5]. Meeting these metrics for ideal CV health is associated with lower CV disease risk, CV

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mortality, and all-cause mortality among adults in the United States[6,7].

Longitudinal cohort studies report that hypertension (HTN), dyslipidemia, and obesity are common comorbidities in SLE, affecting 30–60% of patients[8,9,10]. Maternal CV health at conception and during early pregnancy has implications for the *in utero* environment. Obesity at conception can lead to alterations in metabolic adjustments during gestation, affecting placental, embryonic, and fetal growth. Increased body fat is associated with increased levels of proinflammatory proteins, and obese women are more likely to enter pregnancy in a state of subclinical inflammation[11,12,13]. In the general population, maternal obesity increases the risk of preeclampsia and delivering a large for gestational age (LGA) infant[14,15,16,17,18].

Studies have shown that HTN is a risk factor for preterm birth in the general population[19,20,21]. Additionally, compared to woman without HTN, women with chronic hypertension have 5.5 times the risk of delivering a preterm, SGA infant and 1.5–1.7 times the risk of delivering a term, SGA infant[19,20,22]. Previous research, although limited, has demonstrated that increased total cholesterol during the first trimester is associated with preterm birth in the general population, with possible modification by maternal inflammation[21,23,24].

It has been theorized that maternal risk factors for CV disease may also be risk factors for fetal growth restriction and fetal programming[25]. Because SLE is a chronic inflammatory disease, it is important to understand the way these CV health factors affect preterm birth and fetal growth during SLE pregnancies, because they could be targeted for improved pregnancy outcomes. The objective of this analysis is to determine the proportion of pregnant women with SLE meeting the AHA's guidelines for ideal CV health and to estimate the effects of poor and intermediate CV health on pregnancy outcomes.

MATERIALS AND METHODS

Study population. The Hopkins Lupus Pregnancy Cohort has prospectively followed pregnant patients with SLE since 1987, with data available through February 2015. All patients met the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE[26,27,28] and were enrolled following informed consent. This study is approved by the University of North Carolina Institutional Review Board (Study #13-3942). Pregnant patients were seen every 4–6 weeks by a single rheumatologist. Weight, BP, SLE disease activity [physician's global assessment of disease activity (PGA) and Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index[29,30]], and laboratory tests were measured at each visit. Laboratory tests included complete blood count, complement levels (C3/C4), autoantibodies, total cholesterol, and urinalysis. Pregnancy outcome data were collected from patients at the first postpartum visit or through telephone or e-mail.

Preconceptional CV health. Given the lack in information on smoking, physical activity, diet, and fasting glucose, preconceptional CV health was defined according to 3 available AHA metrics: BMI, total cholesterol, and BP. The following criteria were used: BMI [poor health (obese): ≥ 30 kg/m^2; intermediate health (overweight): 25–29.9 kg/m^2; ideal health (low/normal BMI): < 25 kg/m^2], total cholesterol (poor health: ≥ 240 mg/dl; intermediate health: 200–239 mg/dl or treated to goal; ideal health: < 200 mg/dl), and BP (poor health: systolic ≥ 140 or diastolic ≥ 90 mmHg; intermediate health: systolic 120–139 or diastolic 80–89 mmHg or treated to goal; ideal health: < 120/< 80 mmHg). Each metric was coded as a categorical variable, with "ideal health" as the referent group. Because of the small sample size, poor health and intermediate health were collapsed into 1 exposure category for total cholesterol and BP. Each metric was also analyzed as a continuous variable.

BMI, total cholesterol, and BP at the most recent clinic visit in the 1 year prior to conception were used to classify CV health. If a clinic visit prior to conception was unavailable, the first measurement taken during the first trimester served as a surrogate for preconception health, because minimal changes during the first trimester have been demonstrated[31,32].

Pregnancy outcomes. Pregnancy outcomes of interest included gestational age at birth and birth weight for gestational age Z score. Gestational age at birth was based on the last menstrual period and categorized as preterm (< 37 weeks) and term (≥ 37 weeks), and analyzed as a continuous variable. Birth weight for gestational age Z score was based on US population reference percentiles of birth weight, stratified by infant sex[33]. Birth weight for gestational age Z score was analyzed as a continuous variable, as well as < 10th percentile (SGA) and > 90th percentile (LGA).

Covariates. Covariates of interest included race, education, age at conception, duration of SLE, and infant birth date (prior to January 1999 and January 1999–February 2015). Medication use [low-dose aspirin, hydroxychloroquine (HCQ), immunosuppressants, prednisone, and prednisone ≥ 7.5 mg/day] was defined as use ever during pregnancy. Clinical characteristics during pregnancy were defined as ever occurring during pregnancy: renal involvement (renal Lupus Activity Index > 1), elevated serum creatinine (> 1 mg/dl), high PGA (PGA ≥ 2), low C3/C4, and anti-dsDNA (ever positive). Organ system damage at conception was measured by the SLICC/ACR Damage Index, with a score of ≥ 1 representing the presence of any damage.

Analysis. Differences in the prevalence of preterm birth, SGA, and LGA among live births by preconceptional CV health were analyzed descriptively by Fisher's exact test. Unadjusted differences in mean gestational age and mean birth weight for gestational age Z score by preconceptional CV health were analyzed by ANOVA. Multivariable logistic regression models estimated OR and 95% CI for the association of each maternal CV health factor and categorical pregnancy outcome of interest. Multivariable linear regression models estimated associations of each maternal CV health factor with continuous outcome measures. To account for correlation between multiple births in the same patient, generalized estimating equations with an exchangeable correlation structure were used[34]. Confounders were assessed based on combined directed acyclic graph minimally sufficient set that was reduced based on a 10% change in β estimates for parsimony. Models with BMI as the exposure were adjusted for prednisone use during pregnancy and patient race, and BP models were adjusted for renal involvement during pregnancy and patient race. For the exposure of total cholesterol, 3 adjusted models were estimated: (1) adjusted for patient race and prednisone use during pregnancy; (2) adjusted for patient race and HCQ use during pregnancy; and (3) adjusted for patient race, prednisone use during pregnancy, and HCQ use during pregnancy. All analyses were conducted with SAS 9.3 (SAS Institute Inc.).

RESULTS

During the study period, there were 515 pregnancies, of which 431 were live births. Pregnancies without any CV metrics available in the 1 year prior to conception or first trimester were excluded (n = 122). Of the 431 births, 309 (72%) had at least 1 CV measure (n = 291 BMI, n = 275 total cholesterol, n = 309 BP). Of the 309 pregnancies included,

63% had a CV health measurement in the 1 year prior to conception; the remaining had the measure during the first trimester. More than 1 singleton live birth per patient was allowed in the analysis (309 births to 261 patients).

A greater proportion of live births excluded from the analysis because of missing CV health data were to black mothers and had a pregnancy outcome date prior to 1999, compared to the selected sample. Additionally, excluded patients had shorter disease duration, lower frequency of HCQ use during pregnancy, and lower frequency of low C3/C4. There were no observed differences in live birth outcomes among included patients compared to excluded patients. Patients with a CV health measurement in the 1 year prior to conception had a longer disease duration and higher frequency of HCQ and immunosuppressant use than patients with a first trimester measurement. No differences were seen in live birth outcomes or classification of CV health among patients with preconception measures compared to patients with first trimester measures.

The majority of the 309 pregnancies included in the analysis were to white mothers, with a median age at conception of 30 years (Table 1). HCQ, prednisone, and immunosuppressant use during pregnancy were reported in 60%, 51%, and 15% of pregnancies, respectively. Immunosuppressant use was almost exclusively limited to azathioprine. There were 95 preterm births (31%), and of the 293 pregnancies with birth weights, 18% were SGA and 4% were LGA (Table 2).

BMI, total cholesterol, and BP were reported to be within the ideal range in 56%, 85%, and 51% of pregnancies, respectively (Figure 1). Patients who had low/normal BMI had higher education, a lower prevalence of renal involvement,

Table 1. Population characteristics in the Hopkins Lupus Pregnancy Cohort. Values are n (%) or median (IQR).

Characteristics	Pregnancies, n = 309	Patients, n = 261
Race		
White	184 (60)	151 (58)
Black	93 (30)	80 (31)
Other	32 (10)	30 (11)
Education, yrs		
High school, ≤ 12	101 (33)	81 (31)
College or university, 13–16	141 (46)	120 (46)
Postgraduate, > 16	67 (22)	60 (23)
Pregnancy outcome date		
Prior to January 1999	117 (38)	
January 1999–February 2015	192 (62)	
Medication use during pregnancy*		
Low-dose aspirin	162 (52)	
Hydroxychloroquine	184 (60)	
Immunosuppressant	48 (15)	
Prednisone	160 (51)	
Prednisone ≥ 7.5 mg/day among prednisone users	116 (73)	
No medications	22 (7)	
Clinical characteristics		
Renal involvement during pregnancy (LAI > 1)	79 (26)	
Elevated serum creatinine during pregnancy, >1	24 (8)	
High PGA during pregnancy (PGA ≥ 2)	49 (16)	
SDI ≥ 1 at conception	114 (37)	
Low C3 during pregnancy	74 (24)	
Low C4 during pregnancy	106 (34)	
Anti-dsDNA+ during pregnancy	115 (37)	
Age at conception, yrs	29.9 (26.7–33.2)	
Disease duration, yrs	5.5 (2.1–9.3)	
Highest PGA during pregnancy (scale 0–3)	1.0 (0.5–1.5)	
SDI at conception	0 (0–3)	
Highest daily prednisone dose during pregnancy, mg	2.5 (0–15.0)	
BMI, kg/m^2	24.3 (21.3–29.2)	
Total cholesterol, mg/dl	162.0 (142.0–184.0)	
Systolic BP, mmHg	116.0 (106.0–126.0)	
Diastolic BP, mmHg	70.0 (64.0–80.0)	

* Categories are not mutually exclusive: women can be in multiple categories; therefore, percentages add up to > 100%. IQR: interquartile range; PGA: physician's global assessment; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; BMI: body mass index; BP: blood pressure.

Table 2. Birth outcomes in the Hopkins Lupus Pregnancy Cohort (n = 309 pregnancies). Values are n (%) or median (IQR).

Outcome	Values
Small for gestational age, n = 293	53 (18)
Large for gestational age, n = 293	12 (4)
Preterm birth	95 (31)
Pregnancy-induced HTN, n = 252	15 (6)
Preeclampsia, n = 257	30 (12)
Cesarian section, n = 256	100 (39)
Premature rupture of membranes, n = 255	39 (15)
Gestational age at birth, weeks	38.0 (36.0–39.0)
Birth weight percentile, n = 293	31.0 (12.0–53.0)
Birth weight Z score, n = 293	–0.51 (–1.20 to 0.06)
Birth weight, g, n = 293	2920.0 (2506.1–3309.0)

IQR: interquartile range; HTN: hypertension.

lower BP, and were more frequently nonblack, compared to overweight and obese women. Patients with ideal total cholesterol had higher education, higher frequency of HCQ use, and lower BMI, compared to patients with intermediate/poor total cholesterol. Patients with ideal BP had higher education, lower frequency of prednisone use, lower PGA, lower BMI, and were more frequently nonblack, compared to patients with intermediate/poor BP.

In descriptive models, there was a lower frequency of preterm birth among patients who were obese (20%) compared to patients who were overweight and had low/normal BMI (39% and 31%, respectively). Frequency of SGA was lowest in patients who were overweight (8%) compared to obese and low/normal BMI (22% and 21%, respectively). The frequency of preterm birth was highest in patients with poor total cholesterol (75%) compared to patients with intermediate and ideal total cholesterol (38% and 27%, respectively). The mean gestational age at birth was lower in patients with poor BP (35.8 weeks) compared to patients with intermediate and ideal BP (36.4 weeks and 37.4 weeks, respectively; Table 3). In a sensitivity analysis of only patients with a pre-pregnancy CV measurement (n = 195), there were no differences in the associations between CV health and pregnancy outcomes (data not shown).

In adjusted analyses for race and prednisone use (Table 4), overweight was associated with decreased odds of SGA compared to low/normal BMI (OR 0.26, 95% CI 0.11–0.63). In linear regression models, after adjusting for race and prednisone use, gestational age at birth increased with each 1 kg/m^2 increase in BMI (β 0.06, 95% CI 0.001–0.11), and overweight was associated with a higher birth weight-for-gestational-age Z score (β 0.32, 95% CI 0.06–0.59; Table 5).

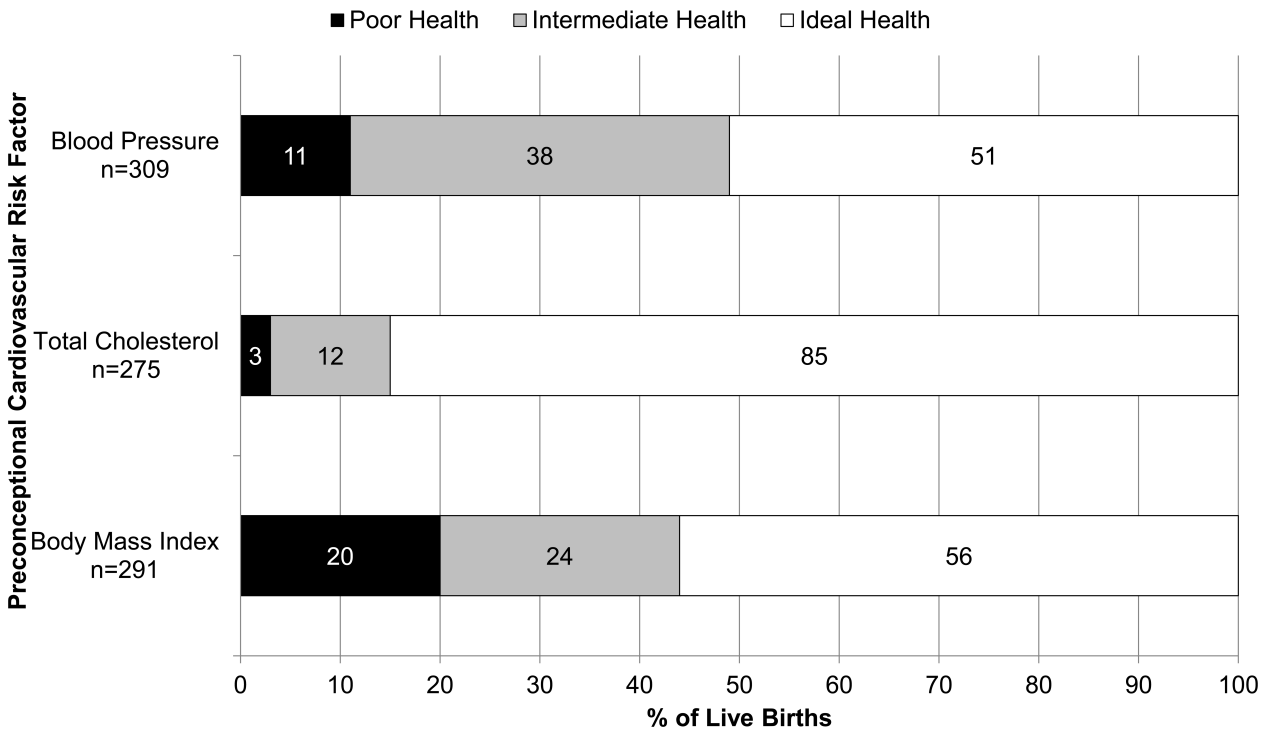

Figure 1. Preconceptional cardiovascular health according to American Heart Association criteria* in the Hopkins Lupus Pregnancy Cohort (n = 309 pregnancies). *BMI: poor health (obese) ≥ 30 kg/m^2, intermediate health (overweight) 25–29.9 kg/m^2, ideal health (low/normal BMI) < 25 kg/m^2; total cholesterol: poor health ≥ 240 mg/dl, intermediate health 200–239 mg/dl or treated to goal, ideal health < 200 mg/dl; blood pressure: poor health (systolic ≥ 140 or diastolic ≥ 90 mmHg), intermediate health (systolic 120–139 or diastolic 80–89 mmHg or treated to goal), ideal health < 120/< 80 mmHg. BMI: body mass index.

Table 3. Mean gestational age and birth weight Z scores by preconceptional CV health*, with ANOVA tests for differences in means in the Hopkins Lupus Pregnancy Cohort (n = 309 pregnancies). Values are mean (SD) unless otherwise specified.

CV Health	Gestational Age	Birth Weight Z Score
BMI		
Ideal health (low/normal BMI)	36.7 (3.9)	–0.58 (0.92)
Intermediate health (overweight)	36.8 (2.6)	–0.28 (0.82)
Poor health (obese)	37.4 (3.1)	–0.51 (1.06)
ANOVA p value	0.3	0.09
Total cholesterol		
Ideal health	37.0 (3.2)	–0.48 (0.94)
Intermediate health	36.8 (2.3)	–0.48 (0.95)
Poor health	34.9 (3.9)	–0.53 (0.60)
ANOVA p value	0.2	1.0
BP		
Ideal health	37.4 (2.6)	–0.48 (0.98)
Intermediate health	36.4 (3.3)	–0.50 (0.91)
Poor health	35.8 (4.1)	–0.55 (0.72)
ANOVA p value	0.003	0.9

* BMI: poor health (obese): ≥ 30 kg/m^2, intermediate health (overweight): 25–29.9 kg/m^2, ideal health (low/normal BMI): < 25 kg/m^2; total cholesterol: poor health: ≥ 240 mg/dl, intermediate health: 200–239 mg/dl or treated to goal, ideal health: < 200 mg/dl; BP: poor health (systolic ≥ 140 or diastolic ≥ 90 mmHg), intermediate health (systolic 120–139 or diastolic 80–89 mmHg or treated to goal), ideal health < 120/< 80 mmHg. BMI: body mass index; CV: cardiovascular; BP: blood pressure.

Additional adjustment for low-dose aspirin use during pregnancy in these models did not change the point estimates.

In logistic regression models adjusted for race and antimalarial use (Table 4), intermediate/poor total cholesterol was associated with increased odds of preterm birth (OR 1.91, 95% CI 0.96–3.79). No association was seen between cholesterol and SGA. In linear regression models (Table 5), no associations were observed between total cholesterol and gestational age at birth or birth weight for gestational age Z score. Additional adjustment for disease activity in these models did not affect the results.

The odds of preterm birth were only slightly increased and were not significant for patients with intermediate/poor BP in logistic regression models (Table 4) after adjustment for race and renal involvement (OR 1.10, 95% CI 0.67–1.79), and no association was observed between BP and SGA. However, in linear regression models (Table 5), intermediate/poor BP was associated with decreased gestational age at birth (β –0.96, 95% CI –1.62 to –0.29), adjusted for race and renal involvement.

DISCUSSION

The analysis highlights the importance of patients with SLE having BMI, total cholesterol, and BP within the ideal range prior to pregnancy to improve pregnancy outcomes. In unadjusted analyses, women with ideal weight, cholesterol, or BP had fewer preterm deliveries, and the mean gestational

Table 4. Multivariable logistic regression models for association of preconceptional CV health and pregnancy outcomes in SLE in the Hopkins Lupus Pregnancy Cohort (n = 309 pregnancies).

CV Health	Preterm Birth		SGA	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
BMI*				
Ideal health (low/normal BMI), n = 163	1.0	1.0	1.0	1.0
Intermediate health (overweight), n = 69	1.39 (0.82–2.36)	1.38 (0.70–2.71) §	0.35 (0.15–0.82)	0.26 (0.11–0.63) §
Poor health (obese), n = 59	0.56 (0.28–1.13)	0.50 (0.21–1.18) §	0.95 (0.44–2.05)	0.92 (0.42–2.05) §
Total cholesterol †				
Ideal health, n = 235	1.0	1.0	1.0	1.0
Intermediate/poor health, n = 40	2.27 (1.15–4.46)	2.21 (1.06–4.62) §	0.57 (0.21–1.54)	0.41 (0.14–1.26) §
		1.91 (0.96–3.79) ‖		0.58 (0.21–1.61) ‖
		1.93 (0.92–4.04) ¶		0.44 (0.14–1.38) ¶
BP ‡				
Ideal health, n = 158	1.0	1.0	1.0	1.0
Intermediate/poor health, n = 151	1.32 (0.82–2.12)	1.10 (0.67–1.79) #	0.68 (0.39–1.20)	0.60 (0.33–1.10) #
Continuous variables				
BMI, kg/m^2 (n = 291)	0.97 (0.93–1.01)	0.95 (0.91–1.00) §	0.99 (0.94–1.04)	0.98 (0.93–1.04) §
Total cholesterol, 10 mg/dl (n = 275)	1.11 (1.03–1.19)	1.10 (1.01–1.19) §	0.91 (0.82–1.02)	0.90 (0.80–1.01) §
		1.08 (1.01–1.16) ‖		0.92 (0.82–1.02) ‖
		1.09 (1.00–1.18) ¶		0.90 (0.80–1.01) ¶
Systolic BP, 10 mmHg (n = 309)	1.15 (0.99–1.34)	1.08 (0.92–1.28) #	0.88 (0.73–1.06)	0.85 (0.70–1.04) #
Diastolic BP, 10 mmHg (n = 309)	1.25 (0.99–1.58)	1.18 (0.93–1.50) #	0.79 (0.59–1.06)	0.75 (0.56–1.02) #

* BMI: poor health ≥ 30 kg/m^2; intermediate health 25–29.9 kg/m^2; ideal health < 25 kg/m^2. † Total cholesterol: poor health ≥ 240 mg/dl; intermediate health 200–239 mg/dl or treated to goal; ideal health < 200 mg/dl. ‡ BP: poor health (systolic ≥140 or diastolic ≥ 90 mmHg); intermediate health (systolic 120–139 or diastolic 80–89 mmHg or treated to goal); ideal health < 120/< 80 mmHg. § Adjusted for race (black vs nonblack) and prednisone use ever during pregnancy. ‖ Adjusted for race (black vs nonblack) and antimalarial use ever during pregnancy. ¶ Adjusted for race (black vs nonblack), prednisone use ever during pregnancy, and antimalarial use ever during pregnancy. # Adjusted for race (black vs nonblack) and renal involvement during pregnancy (Renal LAI ≥ 1). SLE: systemic lupus erythematosus; SGA: small for gestational age; AOR: adjusted OR; BMI: body mass index; LAI: Lupus Activity Index; CV: cardiovascular; BP: blood pressure.

Table 5. Multivariable linear regression models for association of preconceptional CV health and pregnancy outcomes in SLE in the Hopkins Lupus Pregnancy Cohort (n = 309 pregnancies).

CV Health	Gestational Age		Birth Weight for Gestational Age Z Score	
	β (95% CI)	Adjusted β (95% CI)	β (95% CI)	Adjusted β (95% CI)
BMI*				
Ideal health (low/normal BMI), n = 163	Ref	Ref	Ref	Ref
Intermediate health (overweight), n = 69	0.19 (–0.65 to 1.01)	0.14 (–0.63 to 0.93)§	0.29 (0.03–0.56)	0.32 (0.06–0.59)§
Poor health (obese), n = 59	0.75 (–0.21 to 1.71)	0.70 (–0.24 to 1.65)§	0.08 (–0.24 to 0.41)	0.14 (–0.18 to 0.45)§
Total cholesterol †				
Ideal health, n = 235	Ref	Ref	Ref	Ref
Intermediate/poor health, n = 40	–0.53 (–1.46 to 0.40)	–0.43 (–1.28 to 0.41)§	0.02 (–0.29 to 0.33)	0.03 (–0.28 to 0.34)§
		–0.39 (–1.30 to 0.51)‖		–0.02 (–0.32 to 0.29)‖
		–0.37 (–1.22 to 0.48)¶		–0.02 (–0.33 to 0.30)¶
BP ‡				
Ideal health, n = 158	Ref	Ref	Ref	Ref
Intermediate/poor health, n = 151	–1.14 (–1.83 to –0.45)	–0.96 (–1.62 to –0.29)#	0.02 (–0.19–0.24)	0.09 (–0.12 to 0.31)#
Continuous variables				
BMI, kg/m^2 (n = 291)	0.05 (–0.004 to 0.11)	0.06 (0.001–0.11)§	0.01 (–0.01 to 0.03)	0.02 (–0.01 to 0.04)§
Total cholesterol, 10 mg/dl (n = 275)	–0.07 (–0.18 to 0.04)	–0.06 (–0.15 to 0.04)§	0.01 (–0.02 to 0.03)	0.01 (–0.02 to 0.04)§
		–0.06 (–0.16 to 0.04)‖		0.004 (–0.02 to 0.03)‖
		–0.05 (–0.14 to 0.04)¶		0.005 (–0.02 to 0.03)¶
Systolic BP, 10 mmHg (n = 309)	–0.46 (–0.71 to –0.21)	–0.39 (–0.63 to –0.15)#	0.004 (–0.06 to 0.07)	0.03 (–0.04 to 0.10)#
Diastolic BP, 10 mmHg (n = 309)	–0.60 (–0.98 to –0.22)	–0.52 (–0.89 to –0.14)#	0.01 (–0.09 to 0.11)	0.04 (–0.06 to 0.15)#

* BMI: poor health ≥ 30 kg/m^2; intermediate health 25–29.9 kg/m^2; ideal health < 25 kg/m^2. † Total cholesterol: poor health ≥ 240 mg/dl; intermediate health 200–239 mg/dl or treated to goal; ideal health < 200 mg/dl. ‡ BP: poor health (systolic ≥140 or diastolic ≥ 90 mmHg); intermediate health (systolic 120–139 or diastolic 80–89 mmHg or treated to goal); ideal health < 120/< 80 mmHg. § Adjusted for race (black vs nonblack) and prednisone use ever during pregnancy. ‖ Adjusted for race (black vs nonblack) and antimalarial use ever during pregnancy. ¶ Adjusted for race (black vs nonblack), prednisone use ever during pregnancy, and antimalarial use ever during pregnancy. # Adjusted for race (black vs nonblack) and renal involvement during pregnancy (Renal LAI ≥ 1). SLE: systemic lupus erythematosus; BMI: body mass index; LAI: Lupus Activity Index; BP: blood pressure; CV: cardiovascular.

age at birth increased when preconceptional BP was in the ideal range.

In the general population, an analysis of women of reproductive age (20–44 yrs) from the National Health and Nutrition Examination Survey estimated the prevalence of overweight and obesity in the US 2003–2008 to be 23% and 29%, respectively[35]. Our cohort had a similar distribution of pre-pregnancy BMI, with 24% and 20% of women overweight and obese, respectively. Analyses of the Nationwide Inpatient Sample reported that the diagnosis of HTN prior to pregnancy is more common among women with SLE than women without SLE[3]. Additionally, among women who gave birth in the United States in 2002, women with SLE had almost 3 times the prevalence of hypertensive disorders than the general population, with 8% of the general population having a hypertensive disorder[36]. As expected, the prevalence of poor and intermediate prepregnancy BP was high in this cohort, with about half of patients having BP ≥ 120/≥ 80 mmHg or BP treated to goal.

The effects of preconceptional CV health on preterm birth seen in this analysis were consistent with studies of the general population. In the general population, there is a U-shaped association of prepregnancy BMI and preterm birth, with the frequency of preterm birth highest among underweight women and obese women[16,37]. It is important to note, however, that the indication for preterm birth should be considered. Several studies have demonstrated an increased risk of indicated preterm birth but decreased risk of spontaneous preterm birth in obese patients[38,39,40]. Although data are limited, studies have reported that 70–75% of preterm births in women with SLE are medically indicated[41,42]. Reasons for a medically indicated preterm delivery in SLE include maternal BP, preeclampsia, proteinuria, decreased amniotic fluid volume, intrauterine growth restriction, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and SLE flare[43]. A limitation of the present analysis is data specifying indication for preterm births were not collected; therefore, we were unable to determine whether preconception CV health increased the risk of spontaneous preterm birth, indicated preterm birth, or both.

Our finding of increased risk of preterm birth in patients with intermediate and poor preconception cholesterol is supported by previous general population studies. The Coronary Artery Risk Development in Young Adults (CARDIA) study reported a U-shaped association of prepregnancy cholesterol and preterm birth, with the lowest and highest tertiles of prepregnancy cholesterol increasing the risk of preterm birth[44]. This association was supported by a case-control analysis in the Pregnancy Exposures and Preeclampsia Prevention (PEPP) study, which found the risk of preterm birth in patients with high cholesterol during the

first 15 weeks of pregnancy to be almost 3 times the risk of patients with normal cholesterol[23].

The results of our linear regression models show a decrease in gestational age at birth in patients with intermediate and poor preconception BP. This supports previous findings in both the general population and SLE cohorts that HTN is associated with gestational age at birth[19,20,21,45].

Infant size did not appear to be associated with maternal cholesterol or BP, but overweight women had the fewest SGA infants. In adjusted models, overweight women had an almost 40% increased risk of preterm birth compared to low/normal BMI women; however, somewhat surprisingly, overweight women had a 74% decreased risk of an SGA infant compared to women with low/normal BMI. In linear models, overweight women had a greater birth weight for gestational age Z score compared to women with low/normal BMI in linear models. While studies show that low-dose aspirin may decrease the risk of preeclampsia and preterm birth among women with a high risk of these complications, additional adjustment for low-dose aspirin use during pregnancy did not change our results. It is possible that our small sample size did not have sufficient power to detect an effect of aspirin use with pregnancy outcomes. Of particular interest, there was no observed difference in the frequency of LGA births by preconceptional BMI, which is in contrast to pregnancies in the general population[17,46,47]. However, because power was limited by the low frequency of LGA births in the analysis, these results should be considered preliminary.

Our study had some limitations. CV health data were not available for all live births in the cohort, and it is unknown how the CV health of these patients differed. Data were also unavailable for the 4 remaining AHA CV metrics (glucose, physical activity, diet, and cigarette smoking); therefore, we were unable to assess the combined effects of CV risk factors. Because these are important factors for pregnancy outcomes in the general population, poor health in each of these metrics may be associated with an increased risk of preterm birth among patients with SLE. Additionally, the data were collected at a single academic center and therefore may not be representative of all patients with SLE. Finally, the sample size of the analytic cohort limited our statistical power, particularly for discrete outcomes (preterm birth, SGA, and LGA). While the cohort was larger than other SLE pregnancy cohorts, the modest sample size did not provide sufficient power to detect small differences in outcomes. Even so, the results of analyses with continuous variable mirrored that of categorical variables, giving us confidence in our results.

The findings of our analysis have important implications for patients with SLE during pregnancy. Of particular interest is the apparent inverse association of preterm birth in obese patients, but an increased risk of preterm birth in overweight patients. This suggests that efforts to normalize maternal weight prior to pregnancy may improve pregnancy outcomes, but the finding warrants further study. Additionally, having a further understanding of patients with SLE who are able to maintain ideal CV health will be important to develop future targeted interventions. Previous studies have found that among patients with SLE, pregnancy increases the risk of future major CV events and a poor pregnancy outcome increases the risk of CV mortality[48]. Interventions to improve the CV health of patients prior to pregnancy would improve pregnancy outcomes, as well as benefit the longterm health of patients with SLE.

To our knowledge, this analysis is the first to examine the AHA's guidelines for CV health in patients with SLE prior to conception, as well as the first to determine the effects of suboptimal preconceptional CV health on live birth outcomes. Our results suggest that ideal CV health, in addition to well managed SLE disease activity, is an important component to a successful pregnancy outcome. This finding underscores the importance of prepregnancy counseling for women with SLE to ensure that prior to pregnancy their CV health is optimized in accordance with the AHA's guidelines, to reduce the risk of preterm births and improve the overall CV health of patients with SLE. Interventions to improve preconceptional CV health may involve weight loss, increased exercise, and appropriate BP control. This analysis increases our perspective on risk factors for pregnancy complications in women with SLE beyond measures of SLE disease activity and management.

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