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Cardiovascular Risks Associated With Pregnancy Among Women with Systemic Lupus Erythematosus

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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ABSTRACT

Systemic lupus erythematosus (SLE) primarily affects women during their reproductive years. It is three times as common among African American women compared to white women. Women may be at risk of poor birth outcomes even in the years before a clinical diagnosis of SLE. Women with SLE also have a higher incidence of cardiovascular disease (CVD) at younger ages. Adverse pregnancy outcomes have been associated with later CVD in the general population, but the relationship between pregnancy and CVD in women with SLE has not been examined. The goal of this dissertation was to characterize the associations between pregnancy and cardiovascular health among women with SLE, with a focus on African American women with SLE.

In **Aim 1**, we evaluated the association between SLE and preterm and small-for-gestational age (SGA) birth among African American women by timing of birth in relation to diagnosis. After adjusting for maternal age, education and parity, compared with the general population, women were at higher risk of giving birth to preterm or SGA infants within three years before their SLE diagnosis but even more so after their SLE diagnosis.

In **Aim 2**, we examined whether parous women with SLE were at a greater risk of hospitalization for CVD compared to nulligravid women with SLE. Our results suggested a modestly increased hazard of CVD among parous women with SLE compared with nulligravid women with SLE after adjusting for markers of SLE severity.

In **Aim 3**, we examined whether subclinical markers of cardiovascular health, specifically blood pressure, carotid intima media thickness (IMT) and arterial distensibility were associated with parity among African American women with SLE and without SLE. Parity was not associated with blood pressure or IMT among women with SLE, but distensibility was lower among parous women compared to nulliparous women with SLE. There was no association among women without SLE.

This work provides evidence for the need to monitor and coordinate care for all women with SLE, but especially parous women, in order to manage their risk for CVD.

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Table of Contents

List of Figures

List of Tables

Chapter 1 Overview and Specific Aims

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder involving the production of autoantibodies that cause damaging inflammation, affecting multiple organ systems. About 90% of affected persons are women, who are usually diagnosed during their reproductive years [1]. While women with SLE are no longer discouraged from attempting pregnancy, much remains to be understood about risks surrounding pregnancy in women with SLE [2].

Despite the fact that African American women are at 3 times the risk of SLE and are at greater risk of adverse pregnancy outcomes compared to white women, few studies specifically examine adverse birth outcomes among African American women with SLE [3-7]. In addition, risks of cardiovascular complications after pregnancy are not well studied among women with SLE. Women with SLE have a cardiovascular event on average 10 years earlier and cardiovascular death 14 years earlier than women without SLE, irrespective of race [8]. Among women with SLE, it is possible that pregnancy and childbirth may act as stressors that cause inflammation and increase women's risk for cardiovascular disease (CVD). Flares of disease activity can increase in pregnancy [9]. Women with SLE are more likely to experience cardiovascular disease after delivery than women without SLE [10]. Subclinical cardiovascular health has also not been examined among women with SLE, even though it has been shown to be associated with adverse birth outcomes in the general population [11-14].

Public Health Importance

As treatments and life expectancy for people with SLE improve, more women living with SLE will attempt pregnancy and childbearing. The overall goal of this research is to characterize the unique associations between pregnancy and cardiovascular health among women with SLE,

with a particular focus on African American women. This research has the potential to contribute to informing the care of women with SLE before, during and after pregnancy [10, 15].

In the general population, there is greater recognition that pregnancy represents an important opportunity to identify women at elevated risk of CVD, with an emphasis on intervening for young women with adverse birth outcomes [16]. In women with SLE, there is an even greater need to identify the risks surrounding pregnancy and childbirth, particularly among African American who separately stand at greater risk of SLE, adverse birth outcomes, and cardiovascular disease. In the proposed dissertation, we will examine the risk of adverse perinatal outcomes among African American women with SLE and examine parity as a risk factor that may place women with SLE at a uniquely high risk of CVD. Together, all three aims serve to inform the care and management of women with SLE before and after pregnancy.

Specific Aims

Aim 1: Evaluate the association between SLE and the adverse perinatal outcomes preterm birth and small-for-gestational age (SGA) among African American women.

Hypothesis: In women with SLE, births before diagnosis, and to a greater extent, births after diagnosis, have a higher risk of both preterm birth and SGA compared with births to women without SLE.

Aim 2: Examine whether parous women with SLE are at a greater risk of later hospitalization for CVD compared to nulliparous women with SLE.

Hypothesis: Women with SLE who gave birth have an increased risk of hospitalization for later CVD compared with women with SLE who never gave birth.

Aim 3: Examine whether there is an association between parity and blood pressure, carotid intima media thickness and distensibility among African American women with SLE. Sub-aim: Identify if this association is unique or stronger among women with SLE by also conducting the same analyses among a group of comparison women without SLE.

Hypothesis: Parous women with SLE have higher blood pressure and carotid intima media thickness and lower distensibility than nulliparous women with SLE. This association is stronger among women with SLE compared to women without SLE.

Data Sources

Georgia Lupus Registry/Georgians Organized Against Lupus Cohort

The Georgia Lupus Registry (GLR) is a population-based registry of individuals living with SLE in 2002-2004 in Fulton and DeKalb counties in Georgia. Both incident and prevalent cases were identified during this time period. SLE cases were primarily identified from hospitals, rheumatology, nephrology and dermatology groups in and around the catchment area. Administrative databases were also queried retrospectively. To be considered a case, individuals had to either meet ≥ 4 of the revised American College of Rheumatology (ACR) Criteria or 3 of the ACR criteria and have a diagnosis of SLE by the individual's board-certified rheumatologist documented in the medical record [3]. Date of diagnosis was the earliest date that participants were assigned a diagnosis by their treating physician in the medical record.

The Georgians Organized Against Lupus (GOAL) Cohort is an ongoing cohort that originally began recruitment from the GLR, and has since enrolled additional patients with SLE using the same case definition as the GLR from hospitals and clinics in the Atlanta area. Beginning in 2011 and through 2018, participants completed annual surveys covering topics related to physical and mental health. Reflecting the racial distribution of SLE in the Atlanta metropolitan area, about 80% of the participants in both the GLR and GOAL are African American [3, 17].

VISTA

For Aim 3, we used data collected as part of VISTA. In VISTA, African American women with SLE ages 20 – 50 were recruited from the GOAL Cohort. African American women without SLE ages 20 – 50 were recruited from marketing lists to reflect the geographic distribution of women with SLE recruited from GOAL. All women self-identified as African American, were premenopausal and did not have a history of clinical CVD at the time of study enrollment. Women without SLE enrolled into the comparison group were also free of any other autoimmune or chronic inflammatory diseases. All participants attended a clinic visit and completed a questionnaire on demographics, reproductive and health history, behaviors and experiences of stress and support. Participants had their height, weight and blood pressures measured by trained study staff. At this visit, participants also had a carotid ultrasound assessment.

Administrative Data Linkages

Female participants in GLR/GOAL were linked to Georgia birth certificates from 1994 – 2018 on which they are identified as the mother. Data linkages were conducted by the Georgia Department of Public Health (GA DPH). The GA DPH used a multi-stage matching algorithm using combinations of various identifying keys. The identified sample of birth certificates consisted of births both before and after SLE diagnosis. A comparison set of birth certificates to the general population that reflected the racial, age and geographic distribution of the SLE sample was obtained from the National Center for Health Statistics.

Participants in GLR/GOAL were also linked to Georgia inpatient hospital discharge records from 2000-2013. The linkage was conducted by the GA DPH using the same methods as the birth certificate linkage. Discharge records also contain a principal diagnosis and 9 secondary diagnoses indicating the reason(s) for the hospitalization. Diagnoses are coded using the International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM).

Finally, participants in the GLR/GOAL were also linked to death records in the National Death Index (NDI). Death records contain date of death and causes of death identified by ICD-10 codes.

Chapter 2 Background

Description and Epidemiology of SLE

Systemic lupus erythematosus (SLE) can have multiple manifestations, commonly affecting the heart, skin, joints, kidneys and eyes, and can cause progressive, permanent damage to these organs [18, 19].The disease is characterized by periods of quiescence, and periods of flare-ups where autoimmune functioning and inflammation is highly active [20]. Diagnosis of SLE is usually made by a rheumatologist. For the purposes of classification, the American College of Rheumatology has identified a set of eleven criteria to that are characteristic of SLE, including malar or discoid rashes, photosensitivity, renal or neurological disorders or the presence of autoantibodies in a blood test [21]. Individuals with SLE usually meet three or more of the criteria. Because SLE can manifest differently across individuals, diagnosis is often delayed even after the development of clinical symptoms [22]. However, individuals who will eventually be diagnosed with SLE can exhibit autoimmune abnormalities typical of individuals with SLE up to three years before the clinical onset of SLE [23, 24].

National prevalence estimates of SLE are difficult to ascertain, but the most recent national estimate is that 320,000 people have definite or probable SLE in the United States [25]. Women are 9 times as likely to be affected compared to men, and among women, the incidence among African American women is 3 times the incidence among white women [3, 4, 6, 7]. SLE is relatively rare, with a prevalence less than 100 per 100,000 people, but recent estimates suggest that the incidence is increasing, likely due to improved diagnosis [1]. Even with advances in treatment, individuals with SLE remain at a higher risk of death than the general population. The age-standardized mortality ratio among women with SLE has improved since 2000, but the median age of death of women with SLE remains 22 years earlier than women without SLE [26, 27]. Beyond sex and racial disparities, risk factors for SLE are unclear, though genetic, hormonal and behavioral factors have all been implicated [18].

SLE and Birth Outcomes

As SLE is primarily diagnosed among women, and primarily diagnosed between the ages of 15-45, pregnancy outcomes among women with SLE are of interest [1]. Before improvements in treatment for women with SLE, women were discouraged from attempting pregnancy and childbearing. It is now believed that with proper timing and disease management, women with SLE can have successful pregnancies [2]. However, women with SLE still experience higher rates of adverse pregnancy outcomes. Preterm birth, small-for-gestational age, preeclampsia, fetal and maternal death are all more common among women with SLE than women without SLE [28-35]. The risk of preterm birth among women with SLE is consistently twice the risk among women without SLE [36]. On the extreme end of the outcome spectrum, the risk of fetal death has been reported to be 180 per 10,000 deliveries (compared with 65 per 10,000 deliveries to women without SLE) and the risk of maternal death is 180 per 100,000 hospital admissions among women with SLE (compared with 12 per 100,000 among women without SLE) [37]. With a handful of exceptions, most of these studies do not provide estimates for these associations specifically among African American women with SLE [31, 38, 39].

While the absolute risk of extreme outcomes such as fetal and maternal mortality remain low among women with SLE, the high risk of more common outcomes such as preterm birth (25-30% of SLE pregnancies) remains concerning [32, 34, 35, 40]. Small-for-gestational age (SGA) is used as a population level proxy of intrauterine growth restriction (IUGR), which can only be measured by successive ultrasounds in utero. SGA identifies infants born both term and preterm who may be, but are not necessarily, growth restricted [41]. The estimates for small-for-gestational age and intrauterine growth restriction are less consistent in SLE pregnancies, in part because definitions vary across studies, but some indicate the risk of small-for-gestational age is nearly 20% of SLE births, compared to 10% in the general population [29, 32]. Infants

born preterm or small-for-gestational age or growth restricted are vulnerable to poor perinatal outcomes, including infant respiratory issues, infection and slow weight gain and poor childhood outcomes, including stunted growth and impaired cognitive development [42, 43].

Despite the interest in pregnancy outcomes among women with SLE, several important limitations in the literature remain. In U.S.-based studies comparing the risk of birth outcomes in SLE population with women without SLE, SLE populations are primarily identified from one of two sources: large administrative databases or obstetric and/or rheumatology units from individual providers. Studies that draw patients from administrative databases identify women with SLE by the presence of the International Classification of Diseases (ICD)-9 code 710.0 in discharge records [28, 30, 37, 39, 44, 45]. In studies that have validated the use of the ICD code against medical record abstraction in the general population, the positive predictive value of the ICD code alone was approximately 60%, suggesting that a number of SLE cases identified by the code are not true cases [46]. Conversely, study populations drawn from individual providers may include SLE patients with validated diagnoses, but they are patients from single tertiary care centers. These study populations may not reflect the experience of a larger population of women with SLE, are small studies and largely white when conducted in U.S. populations [29, 35, 40, 47-49].

Additionally, individuals who will eventually be diagnosed with SLE can exhibit autoantibodies, including antinuclear antibodies and anti-double-stranded DNA, three years before a clinical diagnosis [23, 24]. However, perinatal outcomes prior to an SLE diagnosis are often not considered. SLE itself can also be challenging to diagnose, often resulting in delayed diagnosis and entry into treatment [22]. Whether due to subclinical manifestations of the disease or delayed diagnosis, the risk of adverse birth outcomes may be elevated in women who will eventually be diagnosed with SLE. Two cohort studies designed to examine perinatal outcomes among women with SLE did not include births prior to SLE diagnosis [50, 51]. We could only find 5 studies that examined birth outcomes both before and after SLE diagnosis that also

included a comparison group (Table 1). Two of these studies are from the early 1990's, and may not reflect current practices in counseling SLE pregnancies. Only 2 used statistical modeling to compare the risks of adverse birth outcomes before and after SLE diagnosis to the risks among healthy women while controlling for potential confounders [31, 52]. Dhar et al. and Arkema et al. only included first pregnancies in their analyses. Barnado et al., Petri et al. and Julkunen et al. included multiple pregnancies per woman, but did not discuss how they accounted for the clustered nature of the data, potentially over-estimating the precision of their results. With the exception of Barnado et al., none of these studies provide estimates specifically among African American women.

Table 2-1. Summary of studies evaluating pregnancy outcomes in women with SLE both before and after diagnosis and including a comparison group

Study	Study Population	Sample Size	PTB and SGA findings
Julkunen, 1993 [52]	Helsinki University Central Hospital (racial distribution not described)	134 pregnancies before SLE diagnosis; 105 pregnancies after SLE diagnosis; 417 pregnancies to women without SLE	PTB before diagnosis: RR 1.5 (95% CI: 0.7, 3.4) PTB after diagnosis: RR 5.8 (3.2, 10.5) SGA before diagnosis: RR 4.8 (95% CI: 1.6, 14.5) SGA after diagnosis: RR 8.6 (3.0, 24.3)
Petri, 1993* [40]	Patients in the Johns Hopkins Lupus Cohort and their friends and relatives, USA (59.0% of SLE patients were African American)	324 pregnancies before SLE diagnosis; 157 pregnancies after SLE diagnosis; 356 pregnancies to friends without SLE; 566 pregnancies to relatives without SLE	PTB before diagnosis: 6.2% PTB after diagnosis: 24.2% PTB in friend comparison group: 3.9% PTB in relative comparison group: 3.7% No SGA results
Dhar, 2005 [47]	Patients at Wayne State University Hospital in Michigan, USA (72.5% of women before diagnosis, 81.8% of women after diagnosis, and 78.7% of women in control	15 pregnancies before SLE diagnosis; 69 pregnancies after SLE diagnosis; 51,000 pregnancies to women without SLE	PTB before diagnosis: 20% PTB after diagnosis: 27% PTB in control group: 15.4% (p=0.03) SGA before diagnosis: 13.3% SGA after diagnosis: 10.1%

	group were African American)		SGA in control group: 5.5% (p>0.05)
Barnado, 2014 [31]	Self-identified African American Gullah women in South Carolina, USA	337 pregnancies before SLE diagnosis; 147 pregnancies after SLE diagnosis; 694 pregnancies to women without SLE	PTB before diagnosis: OR 1.87 (95% CI: 1.07, 3.28) PTB after diagnosis: OR 4.70 (2.42, 9.13) No SGA results
Arkema, 2016 [32]	Swedish Medical Birth Register (racial distribution not described)	133 pregnancies 2-5 years before diagnosis; 65 pregnancies within 2 years before diagnosis; 551 pregnancies after diagnosis; 12,847 pregnancies to women without SLE	PTB 2-5 years before diagnosis: 16.5% PTB 0-2 years before diagnosis: 30.8% PTB after diagnosis: 23.4% PTB in control group: 6.5% SGA 2-5 years before diagnosis: 14.3% SGA 0-2 years before diagnosis: 18.5% SGA after diagnosis: 14.7% SGA in control group: 3.7%

*Odds ratios were calculated, but only for any SLE pregnancy compared to non-SLE pregnancy, not split up by before and after diagnosis

In addition, in general, African American women with SLE are understudied, even though they represent the group at greatest risk of SLE. A number of studies have demonstrated that the risk of adverse birth outcomes is higher among women diagnosed with SLE. However, there is limited research on pregnancy outcomes among African American women with SLE. We were only able to find a handful of studies that examined the relative risk of adverse birth outcomes specifically among African American populations with SLE (rather than just treating race as a confounding variable), and only one of these included risks for intrauterine growth restriction/SGA [31, 38, 39]. African American women make-up the racial group at greatest risk of SLE and are also at greater risk of adverse birth outcomes than white

women. Therefore, more research is needed to quantify the unique risks African American women with SLE experience in pregnancy.

Adverse Birth Outcomes and Cardiovascular Disease

In recent years, there has been a great deal of attention on the connection between pregnancy and CVD, with pregnancy outcomes even called “a window to future cardiovascular disease” [53]. Across a number of populations, women with pregnancy complications have been shown to have a higher risk of CVD. This association is demonstrated both in the early postpartum period and decades after delivery [10, 53-60]. Most evidence supports the notion that women with certain pregnancy complications or adverse birth outcomes have poor underlying vascular or metabolic health prior to pregnancy which increases their risk for pregnancy complications and cardiovascular disease later in life. In this case, pregnancy serves as a “stress-test” to identify women at higher risk of later cardiovascular disease before any clinical symptoms are present [61].

Preeclampsia and gestational hypertension have shown the strongest associations with later cardiovascular disease, followed by placental abruption, preterm birth and small-for-gestational age [59, 62]. Preeclampsia, intrauterine growth restriction, placental abruption, placental infarction and sometimes preterm birth are clustered together in the literature, under the names “maternal placental syndrome” or “ischemic placental disease” [60, 63]. These indicators are all associated with disorders of placentation, which itself involves vascular remodeling [64]. The abnormal vascular remodeling associated with ischemic placental disease is considered a harbinger of later life cardiovascular disease [61]. It should be noted that while preterm delivery is often indicated in the case of complications such as preeclampsia or placental abruption, spontaneous preterm birth is also associated with later maternal cardiovascular disease [65]. Spontaneous preterm births occur without a comorbidity that is an indication for early delivery, and are the result of preterm labor or premature rupture of

membranes. Many studies on birth outcomes and later cardiovascular disease consider preterm birth separately, as there is not a clear association between spontaneous preterm birth and disorders of placentation [10, 59, 66].

The association between adverse pregnancy outcomes and vascular health is also apparent with subclinical markers of cardiovascular disease. Women with adverse perinatal outcomes including preterm birth and small-for-gestational age births, and hypertensive diseases of pregnancy, have been shown to have increased blood pressure in the decades after delivery compared to women with uncomplicated pregnancies, while distensibility, a marker of arterial stiffness, is associated with higher parity [13, 67, 68]. Subclinical markers of atherosclerosis, especially carotid intima media thickness and coronary artery calcification, have also been shown to be elevated among women who experienced complicated pregnancies or adverse perinatal outcomes [12, 67, 69]. Elevated blood pressure, atherosclerosis and arterial stiffness are associated with cardiovascular disease including myocardial infarction and cerebrovascular accidents among women with SLE [70-74].

SLE and Cardiovascular Health

Individuals with SLE are at an increased risk of cardiovascular disease. Cardiovascular disease is one of the leading causes of death among individuals with SLE [75]. Women with SLE experience cardiovascular disease and cardiovascular death at earlier ages than those without SLE. African American women with SLE experience CVD events 11.9 years before and CVD-related death 19.8 years earlier than African American women without SLE [8]. Heart failure, coronary heart disease, stroke and myocardial infarction have all been shown to occur at early ages among women with SLE [76-79]. As these conditions are fairly uncommon among young healthy women, the magnitude of the relative risk is particularly pronounced among women with SLE under age 50, where women are 50 times as likely to have a myocardial infarction when they have SLE [80-82]. Even prior to clinical CVD, there are disparities in

subclinical cardiovascular health between people with SLE and those without. People with SLE have been shown to have greater intima media thickness (IMT) and coronary artery calcification than people without SLE, and also have more than two times the risk of hypertension [83-86].

There are several lupus-specific pathways that are implicated in the increased risk of CVD among SLE patients. Lupus-related autoantibodies cause inflammation, leading to endothelial injury and contributing to atherosclerosis. Individuals with SLE have highly elevated interferon-I activity, which is associated with atherosclerosis, coronary artery calcification and impaired endothelial repair [87, 88]. SLE disease damage, disease activity, corticosteroid use (itself associated with disease activity) and renal involvement have all be shown to be associated with the progression of atherosclerosis in people with SLE [76]. Atherosclerosis and coronary artery calcification are then associated with the development of clinical cardiovascular disease [70, 71]. Estrogen also plays a role in the development of SLE through the estrogen-receptor-α pathway and is even suspected to be a reason for the sex disparity in the incidence of SLE [89]. However, there is not presently a clear link between estrogen and cardiovascular disease, among women with SLE or in the general population [90, 91].

Pregnancy and Cardiovascular Disease in Women with SLE

Among women with SLE, pregnancy and delivery may serve as stressors that increase women's risk of CVD, regardless of the pregnancy outcome. The incidence of SLE flares is increased during pregnancy and postpartum period [9], and organ damage after pregnancy is increased in certain SLE patients [92]. The risk of adverse renal outcomes after pregnancy has been examined in several studies, 2 specifically in women with lupus nephritis. They did not find an association between chronic kidney disease or end stage renal disease when comparing women with lupus who had given birth to women who had not given birth [93-95].

Women with SLE are at a high risk of adverse birth outcomes and CVD. However, only a handful of studies have examined the association between reproductive factors and later cardiovascular disease in women with SLE (Table 2). Three of these studies examined the

association between adverse perinatal outcomes and hypertensive disorders of pregnancy and cardiovascular among women with SLE [10, 15, 96]. As in the general population, there was a greater risk of cardiovascular events after a pregnancy complicated by adverse perinatal outcomes compared to uncomplicated pregnancies. One study, conducted using Taiwanese national health insurance records, demonstrated that compared with women without SLE, those with SLE are at greater risk of major adverse cardiovascular events, even over a short follow-up period of 4 years [54]. To date, only 1 other study of women with SLE has examined pregnancy and childbirth as potential exposures that may increase the risk of cardiovascular disease [97]. It was also conducted in a Taiwanese population and included 149 women with SLE who gave birth and 446 women with SLE without pregnancy over a mean follow-up period of 7 years. This study found no differences overall in major adverse cardiovascular events between women with SLE who had and who had not given birth. However, it did report an association, albeit imprecise, between giving birth and heart failure among with women with SLE.

Table 2-2. Summary of studies examining cardiovascular disease after pregnancy among women with SLE

Study	Population	Exposure Definition	Outcome Definition	Findings
Soh, 2016 [10]	Women with SLE and history of pregnancy in linked Swedish Medical Birth Register and National Patient Register 1973-2011 (N=3977) (racial distribution not described)	Maternal placental syndrome: hypertensive disorders of pregnancy, stillbirth, SGA, placental abruption; preterm birth (<34 weeks gestation)	Cardiovascular event (CVE) as recorded in the patient register or death from cardiovascular cause	Any MPS was associated with any CVE (adjusted HR: 1.6, 95% CI: 1.3, 2.1); when MPS combined with PTB, magnitude increased (adjusted HR: 2.0, 95% CI: 1.4, 2.8)
Lin, 2014 [15]	Drawn from the parent study Study of Long-term Vascular and Bone Outcomes in Lupus Erythematosus (SOLVABLE) in Chicago (N=129) (racial distribution not described)	Self-reported history (confirmed when possible in medical records) of preeclampsia, preterm birth or low birthweight	Cardiovascular event as recorded in medical records	Odds of CVE not elevated among women with adverse birth outcomes (adjusted OR: 0.6, 95% CI: 0.2, 3.2)
Wu, 2014 [97]	Women with SLE and deliveries identified by delivery discharge codes (n=149) and women without deliveries (n=446) in Taiwanese National Insurance Records 2000 - 2010	Delivery as identified by delivery ICD codes	Major adverse cardiovascular event (MACE), including death, in discharge records	No association between delivery and MACEs overall among women with SLE (adjusted IRR: 1.1, 95% CI: 0.5, 2.3)

Wu, 2014 [54]	Linked Taiwanese birth certificate data and national health insurance records from 1999-2003 and death certificate files (n=1,132,089 women who had given birth)	SLE identified by ICD codes	Major adverse cardiovascular event (MACE) identified by ICD codes (12 in women with SLE, 749 among women without SLE)	SLE was associated with any MACE after delivery (adjusted HRL 9.95, 95% CI: 5.6, 17.7)
Simard, 2021 [96]	Women with SLE (n=450) and a comparison group without SLE (n=2,890) in the Swedish Medical Birth Register 1987-2012	Discharge diagnosis of hypertensive disorders of pregnancy (HDPs) during the first pregnancy	Cardiovascular outcomes as recorded in the Swedish National Patient Register, the Swedish Stroke Register or the Swedish Cause of Death Register	HDPs were associated with cardiovascular events in women with SLE (adjusted HR: 1.9, 95% CI: 0.8, 4.3) and women without SLE (adjusted HR: 1.7, 95% CI: 0.5, 6.0) with no evidence of effect modification by SLE

In the association between adverse birth outcomes and pregnancy complications, most evidence tends to support a common cause hypothesis in the general population, where pregnancy complications and later cardiovascular disease are indicative of underlying vascular health. However, women with SLE are already susceptible to vascular and organ damage [19, 98]. In these women, pregnancy may act as a stressor that increases their later risk of cardiovascular disease. Pregnancy is often associated with an increased risk of SLE flares, which are associated with more SLE-related organ damage [9, 99].

It is important to establish SLE-specific risk factors for CVD among women with SLE. Traditional cardiovascular risk factors, such as high cholesterol, diabetes and hypertension, are not uncommon among women with SLE [84]. However, traditional risk factors fail to account for the substantially higher risk of CVD among women with SLE [100, 101]. Young women in general do not present with the classic symptoms of CVD compared to older women or men [102]. If parity is a risk factor for CVD that is specific to women with SLE, high-risk women with SLE could be flagged immediately after childbirth so that their treatment could be monitored and managed.

Despite advances in the treatment and prognosis of SLE, young women with SLE remain at a high risk of CVD and death. Women with SLE show an increased risk of CVD even before age 50 [80]. African American women with SLE experience cardiovascular-related death

on average 20 years earlier than their non-SLE counterparts [8]. The limited research on CVD after birth among women with SLE has focused on adverse birth outcomes as a risk factor for CVD. There is a need for research that specifically examines parity as a risk factor for CVD and postpartum cardiovascular health. Furthermore, there is a need for research that includes a large population of African American women, who separately are at greater risk of SLE, earlier cardiovascular disease and adverse pregnancy outcomes than white women. Among African American women, after excluding accidental death (deaths due to homicide, suicide and unintentional injury), SLE was the 6th leading cause of disease-related death for ages 25-34 and the 8th leading cause of disease-related death for women age 35-44 based on the contributing cause of death field on death certificates [103]. SLE is a complex disease that, through a number of mechanisms, places women at a high risk of early morbidity and mortality.

Chapter 3 Adverse Perinatal Outcomes Before and After Diagnosis Among Women with Systemic Lupus Erythematosus

Abstract

Objective: Women with systemic lupus erythematosus (SLE) may experience adverse perinatal outcomes in the years before an SLE diagnosis. Overall, there is limited research on perinatal outcomes among African American women with SLE.

Methods: Women with SLE identified from the Georgia Lupus Registry and the Georgians Organized Against Lupus Cohort were linked with birth certificates by the Georgia Department of Public Health. Births were categorized as occurring more than 3 years before SLE diagnosis, 0-3 years before SLE diagnosis, 0-3 years after SLE diagnosis or more than 3 years after SLE diagnosis. Comparison birth certificates to African American women in the same geographic area were obtained from the National Center for Health Statistics. We used log-risk models to compare the risk of preterm birth or small-for-gestational age among SLE births in each diagnosis timing category to the general population, adjusting for maternal age and education and parity.

Results: Births to women with SLE were more likely to occur preterm 0-3 years before SLE diagnosis (risk ratio [RR]: 1.71, 95% confidence interval [CI]: 1.24, 2.35), 0-3 years after SLE diagnosis (RR: 2.29, 95% CI: 1.70, 3.09) and 3 or more years after diagnosis (RR: 2.83, 95% CI: 2.36, 3.38), but not 3 or more years before SLE diagnosis compared to the general population (RR: 1.03, 95% CI: 0.77, 1.38). Similar results were observed for small-for-gestational age births.

Conclusion: Our analysis, conducted among African American women, demonstrates an increased risk of adverse perinatal outcomes even before a clinical diagnosis of SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that commonly affects the heart, skin, joints, kidneys and eyes, and can cause progressive, permanent damage to these organs [18, 19]. The disease is characterized by periods of quiescence, and periods of flare-ups where autoimmune functioning is highly active [20]. Because SLE can manifest differently across individuals, diagnosis is often delayed even after the development of clinical symptoms [22]. However, individuals who will be diagnosed with SLE can exhibit autoimmune abnormalities three years before the clinical onset of SLE [23, 24].

Women are nine times as likely to be diagnosed with SLE compared to men, and among women, the incidence among African American women is 3 times the incidence compared to white women [3, 4, 7]. As SLE is primarily diagnosed among women, and is typically diagnosed during their reproductive years, understanding the effect of SLE on perinatal outcomes is important [1]. Studies suggest that preterm birth, small-for-gestational age, preeclampsia, fetal and maternal death are all more common among women with SLE than women without SLE [28-30, 32-35].

While the risk of extreme outcomes such as fetal and maternal mortality are low among women with SLE, the high risk of more common outcomes, such as preterm birth (25-30% of SLE pregnancies among white women) remains concerning [32, 34, 35, 40]. Several studies have examined racial disparities in perinatal outcomes between African American and white women with SLE. These studies often had few African American participants and therefore examined composite adverse outcomes or used hospital discharge data to examine ICD-9 codes for preterm labor as a proxy for preterm birth [38, 39, 50, 51]. Only one study was large enough to provide estimates for preterm birth but not small-for-gestational age among African American women with SLE [31]. Small-for-gestational age (SGA), though less well-studied than preterm birth, also appears to be elevated among women with SLE. SGA is used as a population-level proxy of fetal growth restriction, which is measured by successive ultrasounds

in utero [43]. The estimates for small-for-gestational age are less consistent in SLE pregnancies, in part because definitions vary across studies, but some indicate the risk of small-for-gestational age is nearly 20% among SLE births to white women, while there are no estimates specifically among African American women [29, 32]. Infants born preterm or small-for-gestational age are vulnerable to poor perinatal outcomes, including infant respiratory issues, infection and slow weight gain and poor childhood outcomes, including stunted growth and impaired cognitive development [42, 43]. Furthermore, several studies have suggested that there is an elevated risk of adverse perinatal outcomes among women with SLE even before their clinical diagnosis [31, 32, 40, 47, 52]. Only one of these studies included a large enough study population to generate estimates for the risk of preterm birth before diagnosis specifically among African American women who later developed SLE.

Despite the interest in pregnancy outcomes among women with SLE, important gaps in the literature remain. There is limited research on preterm birth and SGA specifically among African American women with SLE, and only one study, conducted among a unique population in the Sea Islands of South Carolina, has examined perinatal outcomes before SLE diagnosis among African American women. In the present analysis, we examine the risk of preterm and small-for-gestational age birth among African American women with SLE compared to the general population of African American women in a large metropolitan area. We examine births both before and after the date of SLE diagnosis. We hypothesize that compared to the general African American population, the risk of preterm and SGA births is elevated among African American women with SLE before diagnosis, and elevated to an even greater extent after diagnosis.

Methods

Study Population with Systemic Lupus Erythematosus

Women with SLE were identified from both the Georgia Lupus Registry (GLR) and the Georgians Organized Against Lupus (GOAL) Cohort. The GLR is a population-based registry of individuals living with SLE in 2002-2004 in Fulton and DeKalb counties, the two most populous counties in metropolitan Atlanta, Georgia. Both incident and prevalent cases were identified during this time period. SLE cases were primarily identified from hospitals and rheumatology, nephrology and dermatology groups in and around the catchment area. Administrative databases were also queried retrospectively. To be considered a case, individuals had to either meet ≥ 4 of the revised American College of Rheumatology (ACR) Criteria or 3 of the ACR criteria and have a diagnosis of SLE by a board-certified rheumatologist documented in the medical record [3, 21]. The GLR and GOAL were both approved by the Institutional Review Boards of Emory University and the Georgia Department of Public Health.

The GOAL Cohort is an ongoing cohort that originally began recruitment from the GLR, and has since enrolled additional patients with SLE using the same case definition as the GLR from hospitals and clinics in the Atlanta area. Reflecting the racial distribution of SLE in the Atlanta metropolitan area, about 80% of the participants in both GLR/GOAL are African American [3, 17]. This analysis is restricted to African American female participants in GLR/GOAL to generate reliable estimates for an understudied group of women affected by SLE. This analysis was also restricted to singleton births.

Female participants in GLR/GOAL were linked to Georgia birth certificates from 1994 – 2018 on which they are identified as the mother. The data linkage was conducted by the Georgia Department of Public Health with a multi-stage matching algorithm using combinations of various identifying keys [104].

Comparison Birth Certificates

Birth certificates from the general population between 1994 and 2018 were obtained from the National Center for Health Statistics. All singleton births occurring to African American women in Georgia during the appropriate time frame were identified. Sampling was conducted

to match the distribution of births by year and maternal county of residence to the set of SLE births. Sampling was done to achieve a 1:20 ratio of SLE births to general population births.

Variable Definitions

The exposure of interest was a diagnosis of systemic lupus erythematosus. In GLR/GOAL, a diagnosis of SLE was confirmed by physician review of medical records. When available in GLR/GOAL, the date of diagnosis was captured in medical records. When the medical records were not available, the date of diagnosis was obtained by self-report. Births to women with SLE were categorized as occurring more than three years before diagnosis, within 3 years before diagnosis, within 3 years after diagnosis or more than three years after diagnosis. Women whose diagnoses occurred during pregnancy were categorized as having their births within 3 years after diagnosis.

Preterm birth was defined as a birth occurring before 37 completed weeks of gestation, identified from the clinical best estimate of gestation on the birth certificate. Small-for-gestational-age births were infants born with birthweights below the 10^{th} percentile by gestational age at birth. We used published standards of birthweights by gestational age that were developed from a national dataset of singleton births to non-Hispanic African American mothers [105].

Potential confounders of interest, including maternal age, education, parity and initiation of prenatal care, were obtained from the birth certificate.

Statistical Analysis

Descriptive characteristics of births in each exposure category, including the proportion of births that were preterm or SGA, were summarized using frequencies and percentages. We generated estimated risk ratios using log-risk models. In our data, births to women with SLE have unique identifiers, where we can identify births occurring to the same woman among women with SLE, but in the set of births to the general population, we cannot identify unique women in the data. Since our main analyses were conducted treating all births as independent

events, the precision of the confidence intervals for our estimates is potentially overestimated. We addressed this issue in two ways. First, we conducted a sensitivity analysis that restricted the study population to first births. Second, we conducted a simulation to examine the effect of not accounting for covariance among births in the main analysis. This simulation is described and presented in the Appendix. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, N.C.).

Results

Our final analytical sample included 583 births to African American women with SLE and 11,660 births to African American women in the general population from metropolitan Atlanta. Among women with SLE, the majority of births occurred before SLE diagnosis, with the greatest proportion of all births (40.8%) occurring more than three years before diagnosis (Table 1). The distribution of maternal age at delivery was slightly younger among African American women with SLE compared to the general population of African American women, with 51.3% of SLE births to women under age 25, compared to 46.0% of births in the general population. Women with SLE were likely to initiate prenatal care in the first trimester (72.2% of births), which was similar to the general population (69.7%). About 40% of SLE births and of births in the general population were first births. A noticeably higher proportion of SLE births were delivered by cesarean section (33.1% vs. 24.7%).

Overall, 28.5% of births in our cohort of African American women with SLE were preterm, compared to 15.5% among African American women in the general population. The proportion of births that were preterm among women with SLE increased linearly by timing of the birth in relation to SLE diagnosis, ranging from 16.4% of births more than 3 years before diagnosis to 43.3% of births more than 3 years after diagnosis (Figure 1). The pattern was different when examining SGA births. The risk of SGA birth was 10.9% more than 3 years before diagnosis, but 27.9% within 3 years after diagnosis. By more than 3 years after SLE diagnosis, the proportion of births that were SGA was 21.3% of births. There also was a trend in

the proportion of SLE births that were delivered by cesarean section. Births occurring before SLE diagnosis were about as likely to be delivered by cesarean section as the general population (24.7%), but births occurring within 3 years after diagnosis and more than 3 years after diagnosis were much more likely to be delivered by cesarean section (45.6% and 44.7%) (Figure 2). Preterm births to African American women with SLE were more likely to be delivered by cesarean section than preterm births to women without SLE, especially within 3 years after diagnosis where over 70% of preterm deliveries were by cesarean section, compared to 29% in the general population (Figure 3).

In unadjusted models, births occurring to African American women with SLE more than 3 years before their diagnosis did not have an increased risk of preterm birth compared to the general population (RR: 1.05, 95% CI: 0.79, 1.41) (Table 2). Births occurring within 3 years before diagnosis did have an increased risk of preterm birth compared to the general population (RR: 1.76, 95% CI: 1.28, 2.42). For births to women with SLE occurring after their diagnosis, the risk of preterm birth was more than twice that of the general population. Births more than three years after diagnosis had the highest risk of preterm birth, with a risk ratio of 2.78 (95% CI: 2.32, 3.33). These estimates changed only slightly after adjusting for maternal age, education and parity.

When we restricted the preterm birth models to first births only (and adjusted for maternal age and education), the estimates showed a similar pattern. SLE was not associated with preterm birth more than 3 years before diagnosis (RR: 1.20, 95% CI: 0.77, 1.86), but the relative risk increased for each diagnosis timing category (within 3 years before, within 3 years after, more than 3 years after), with the greatest relative risk occurring among births more than 3 years after diagnosis (RR: 3.56, 95% CI: 2.74, 4.62). The results were also similar when we restricted to vaginal births only.

In the unadjusted models examining the risk of SGA birth, among births to women with SLE more than three years before diagnosis, there was no evidence of an increased risk of

SGA birth compared to the general population of African American women (RR: 1.11, 95%: 0.77, 1.60) (Table 3). Among births to women with SLE occurring within 3 years before diagnosis, the relative risk increased to 2.38 (95% CI: 1.76, 3.51), and to a maximum of 2.82 (95% CI: 1.97, 4.04) when births occurred within 3 years after SLE diagnosis. Although still greater than the general population, the risk of SGA birth was lower among births occurring more than 3 years after diagnosis compared to those occurring closer to the time of SLE diagnosis (RR: 2.16, 95% CI: 1.60, 2.92). When we adjusted for maternal age, education and parity, the estimates were of a similar magnitude and showed the same pattern, with the greatest increased risk among SLE births occurring within 3 years after diagnosis.

We also restricted the adjusted model for SGA to first births only. There was a similar pattern among first births. There does not appear to be an association among women more than 3 years before their SLE diagnosis (RR: 0.85, 95%: 0.47, 1.55), but an increase within 3 years before diagnosis (RR: 2.60, 95%: 1.70, 3.99), the greatest increase in risk observed among births occurring within 3 years after SLE diagnosis (RR: 2.96, 95%: 1.74, 5.03), which then decreased more than three years after diagnosis (RR: 2.15, 95%: 1.37, 3.36). The estimates showed a similar pattern when we restricted the model to vaginal births only.

The results of the simulation analysis presented in the Appendix suggest that the precision of the estimated confidence intervals may have been slightly overestimated, by 3-4%, by not accounting for the covariance of births occurring to the same woman.

Discussion

The births to African American women with SLE in our study population occurred to slightly younger women than births to the general population of African American women. Births to women with SLE were roughly equally likely to have been to women with a college degree and to be first births compared to the general population of African American women. In our analysis, we found an increased risk of preterm birth and SGA birth among African American women with SLE, both in the years immediately before diagnosis of SLE and in the years after

diagnosis. However, we saw a different pattern for preterm births compared to SGA births. The risk of preterm birth was elevated among births occurring within 3 years before diagnosis, 3 years after diagnosis and among births occurring more than three years after diagnosis. The greatest increased risk of SGA occurred in the three years immediately after SLE diagnosis.

Individuals with SLE demonstrate immune abnormalities prior to SLE diagnosis, but perinatal outcomes before diagnosis are not often considered. We could only find five studies that examined perinatal outcomes both before and after SLE diagnosis that also included a comparison group [31, 32, 40, 47, 52]. Two of these studies are from the early 1990's, and may not reflect current practices in counseling SLE pregnancies. Only two used statistical modeling to control for potential confounders. With the exception of Barnado et al., none of these studies provide estimates specifically among African American women. We provide an important replication of Barnado et al.'s findings in a population of African American women in a major metropolitan setting as well as extend their findings to include SGA estimates among African American women with SLE.

All five studies that examined the risk of preterm and/or SGA birth before diagnosis found an increased risk of preterm birth and SGA birth before diagnosis when comparing to a non-SLE cohort. Only one of these studies, Arkema et al., distinguished between births occurring 2-5 years before diagnosis and 0-2 years before diagnosis in a Swedish cohort. This study found the risks of preterm and SGA births were especially elevated 0-2 years before diagnosis. Our results also provide support for an association between a pre-diagnosis state of SLE and adverse perinatal outcomes among African American women who will eventually be diagnosed with SLE. This could be due to immune abnormalities experienced in the years before a clinical diagnosis. Antiphospholipid antibodies and anti-Ro antibodies can both be elevated years before a clinical SLE diagnosis is possible, and have also been shown to be associated with preterm birth [24, 35, 51]. Conversely, the observed association could be due to the symptoms of active SLE, which have been shown to be associated with adverse perinatal

outcomes [106-108]. Diagnosis of SLE is often delayed even after the presentation of clinical symptoms [22].

We could only find one other study that examined the risk of preterm birth before diagnosis specifically among African American women with SLE [31]. Our results were of a similar magnitude as Barnado et al. for births before SLE diagnosis, where they found an odds ratio of 1.87 (95% CI: 1.07, 3.28) for preterm birth, but were less extreme than their results for births after SLE diagnosis, where they found an odds ratio of 4.70 (95% CI: 2.42, 9.13) for preterm birth. Barnado et al. was conducted among Gullah African Americans (220 women with SLE, 217 women without SLE) in the Sea Islands of South Carolina, and the large odds ratio for preterm birth after diagnosis was driven by the low risk of preterm birth in their comparison population, where less than 5% of births were preterm. This low risk of preterm birth is not reflective of the risk of preterm birth among African American women in metropolitan Atlanta (16%), or African American women nationally (14%) [109]. Barnado et al. did not examine SGA births.

We found no other studies that separated births after SLE diagnosis into births occurring in the years immediately following diagnosis and births later after diagnosis, so we cannot compare the differing trend that we saw where the risk of SGA births eventually decreased in the 3 years after SLE diagnosis while preterm births continued to increase. The differing trends may be due to random variability of the data. Conversely, the difference may be due to real factors. While estimates vary, a large proportion of preterm births among women with SLE appear to be medically-indicated, with preeclampsia being a major indicator for preterm delivery [45, 110, 111]. Although preeclampsia may result in medically indicated preterm birth, it does not necessarily affect fetal growth. Other aspects of SLE disease that could affect fetal growth may be more likely to be stabilized more than 3 years after diagnosis, resulting in a lower risk of SGA. We could not distinguish between medically-indicated and spontaneous preterm births in our data, but we did have information on method of delivery from the birth certificate. Studies

suggest that medically indicated preterm births are more likely to be delivered via cesarean section, while spontaneous preterm births are more likely to be delivered vaginally [110, 112]. In our sample, from within 3 years after diagnosis to 3 or more years after diagnosis, the proportion of preterm births delivered by cesarean section, while decreasing slightly, remained high, going from 71% to 59%. When restricting the multivariable analysis to vaginal deliveries only, we saw the same trend where women with SLE were at the greatest risk of preterm delivery more than 3 years after diagnosis. While method of delivery is only a rough proxy for the medical necessity of a preterm delivery, this suggests that medically-indicated preterm births remain common, even after a stable treatment regimen for SLE may be established in the early years after diagnosis.

Some limitations should be noted. Ideally, insurance status and maternal receipt of WIC as listed on the birth certificate would have been part of our analysis as indicators of socioeconomic status. However, in Georgia, these variables were only available on the birth certificate beginning in 2009 which would have rendered our sample size too small to conduct a multivariable analysis. In addition, we used birth certificates from the general population of African American women in Georgia as our comparison group, rather than births to African American women who were confirmed to not have SLE. This set of comparison birth certificates potentially contained births to women with SLE, and we have no way to exclude these births using information from the birth certificate. The estimated prevalence of SLE among African American women in Georgia is 196.2 per 100,000 [3]. With the age distribution of the 11,660 African American women included in our comparison group, the expected prevalence of SLE in our comparison group is approximately 0.20%, or 22 women. We do not expect this to have influenced our results. We also did not have a unique identifier among the comparison births to identify births to the same woman. Our simulation analysis (Appendix) demonstrated that not accounting for births to the same women likely generated estimated confidence intervals that were only 3-4% narrower than what would have been estimated had we been able to account

for the covariance of multiple births to the same woman. Restricting the adjusted analysis to first births also eliminated the issue of covariance, but did not dramatically alter our results. Finally, as previously mentioned, we were unable to differentiate between medically-indicated and spontaneous preterm births.

Our analysis has several strengths. First, we included only validated cases of SLE. Studies that draw patients from administrative databases identify women with SLE by the presence of the International Classification of Diseases (ICD)-9 code 710.0 in discharge records [28, 30, 37, 39, 44, 45]. In studies that have validated the use of the ICD code against medical record abstraction in the general population, the positive predictive value of the ICD code alone was approximately 60%, suggesting that a number of SLE cases identified by the code are not true cases [46]. We also included births to women with SLE both before and after clinical diagnosis and were able to demonstrate that the risks for both preterm birth and SGA are elevated in the years before diagnosis. Finally, our study included a large sample of self-identified African American women with SLE, who have been understudied with respect to perinatal outcomes, yet represent a group at a high risk of SLE.

As the prognosis for women diagnosed with SLE improves, more women with SLE will likely pursue pregnancy and childbearing. Our results suggest that African American women with SLE are at greater risk for the adverse outcomes preterm birth and SGA than the general population of African American women, even before a clinical diagnosis of SLE. In general, African American women have a higher risk of preterm birth and SGA, a greater risk of pregnancy complications that may lead to these outcomes, including preeclampsia and gestational hypertension, and are more likely to die in childbirth than white women [5, 113-115]. More work remains to be done to characterize the additional risks around pregnancy and childbirth that African American women with SLE face. Healthcare providers, especially those serving communities of color should be better educated about SLE, and have a lower threshold to suspect SLE in the peripartum period.

Tables and Figures

Table 3-1. Participant characteristics

Characteristic	SLE births (N=583)	Non-SLE Births (N=11,660)
Timing of Birth		
>3 years before diagnosis	238 (40.8)	
Within 3 years before diagnosis	102 (17.5)	
Within 3 years after diagnosis	79 (13.6)	
>3 years after diagnosis	164 (28.1)	
Preterm		
Preterm	166 (28.5)	1812 (15.6)
Not preterm	417 (71.5)	9829 (84.4)
Small-for-Gestational Age		
SGA	108 (18.5)	1141 (9.9)
Not SGA	475 (81.5)	10426 (90.1)
Maternal Age		
12-19	119 (20.4)	1949 (16.7)
20-24	180 (30.9)	3411 (29.3)
25-29	138 (23.7)	2934 (25.2)
30-34	90 (15.4)	2082 (17.9)
35-39	44 (7.6)	1050 (9.0)
40+	12 (2.1)	234 (2.0)
Prenatal Care Initiation		
First Trimester	421 (72.2)	8122 (69.7)
Second Trimester	88 (15.1)	1890 (16.2)
Third Trimester	11 (1.9)	389 (3.3)
No Prenatal Care	6 (1.0)	293 (2.5)
Unknown	57 (9.8)	966 (8.3)
Parity		
1	238 (40.8)	4571 (39.3)
2-3	263 (45.1)	5182 (44.6)
4+	82 (14.1)	1879 (16.2)
Delivery Method		
Vaginal	390 (66.9)	8756 (75.3)
Cesarean Section	193 (33.1)	2872 (24.7)
Education		
High School or Less	367 (64.2)	6846 (60.1)
Some College	127 (22.2)	2700 (23.7)
College or Higher	78 (13.6)	1841 (16.2)

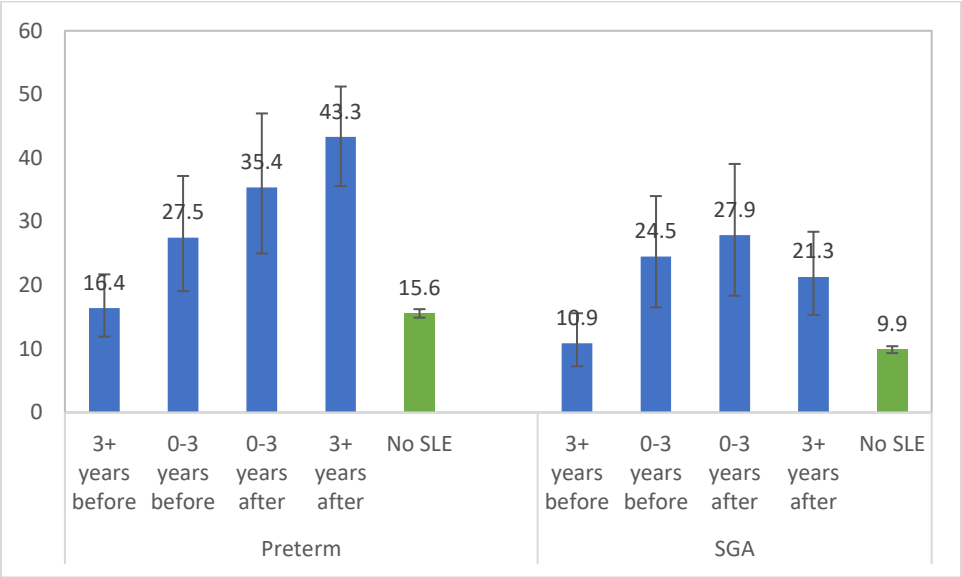

Figure 3-1. Preterm birth and small-for-gestational age by timing of birth in relation to SLE diagnosis among African American women

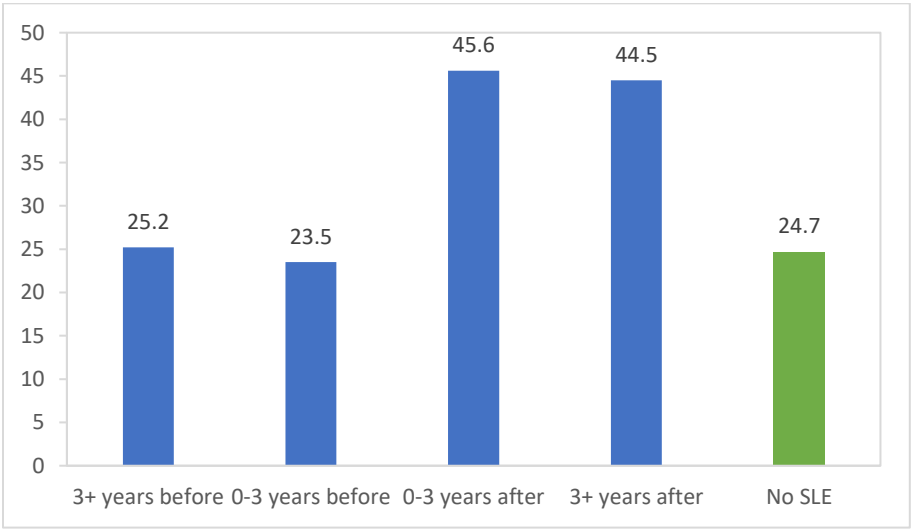

Figure 3-2. Proportion of births delivered by cesarean section by timing of SLE diagnosis among African American women

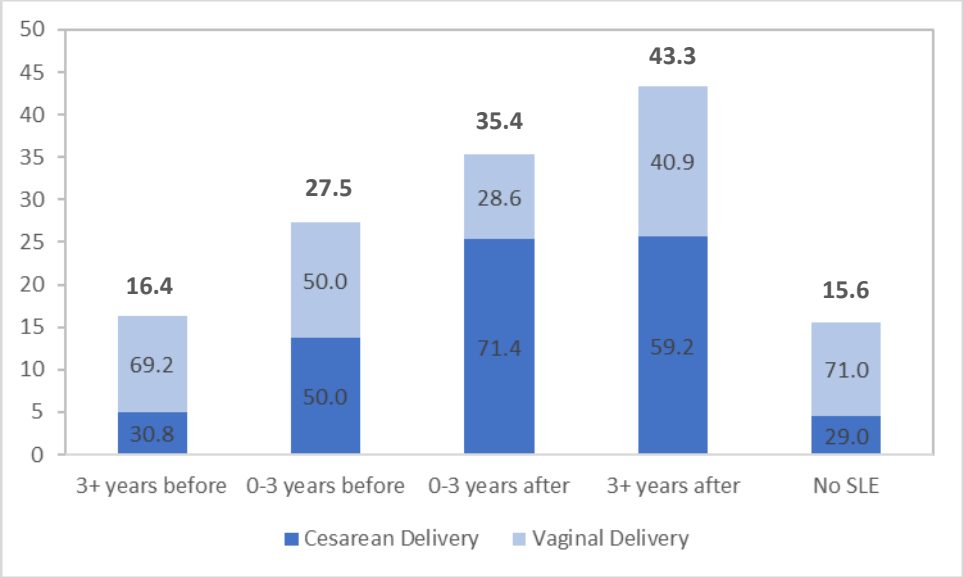

Figure 3-3. Delivery method among preterm births to African American women (overall proportion of births that were preterm in bold)

Table 3-2. Risk ratios modeling the risk of preterm birth among African American women

	Unadjusted	Adjusted*	First births only*	Vaginal births only*
3+years before diagnosis	1.05 (0.79, 1.41)	1.03 (0.77, 1.38)	1.20 (0.77, 1.86)	0.99 (0.69, 1.41)
Within 3 years before diagnosis	1.76 (1.28, 2.42)	1.71 (1.24, 2.35)	1.90 (1.19, 3.04)	1.18 (0.73, 1.90)
Within 3 years after diagnosis	2.28 (1.69, 3.08)	2.29 (1.70, 3.09)	2.75 (1.68, 4.49)	1.30 (0.70, 2.43)
3+ years after diagnosis	2.78 (2.32, 3.33)	2.83 (2.36, 3.38)	3.56 (2.74, 4.62)	2.21 (1.62, 3.01)

*Adjusted for maternal age, education and parity

Table 3-3. Risk ratios modeling the risk of small-for-gestational age

	Unadjusted		Adjusted*	First births only*		Vaginal births only*	
3+years before diagnosis	1.11	(0.77, 1.60)	1.05 (0.72, 1.53)	0.85	(0.47, 1.55)	0.97	(0.61, 1.53)
Within 3 years before	2.48	(1.76, 3.51)	2.38 (1.69, 3.36)	2.60	(1.70, 3.99)	2.39	(1.61, 3.56)
Within 3 years after	2.82	(1.97, 4.04)	2.89 (2.03, 4.13)	2.96	(1.74, 5.03)	2.88	(1.78, 4.67)
3+ years after	2.16	(1.60, 2.92)	2.28 (1.69, 3.07)	2.15	(1.37, 3.36)	1.44	(0.85, 2.45)

*Adjusted for maternal age, education and parity

Appendix: Simulation accounting for covariance

There were no unique identifiers in the set of birth certificates to the general population with which we could identify births occurring to the same woman, but we did have access to these identifiers in the birth certificates to women with SLE. We used the identifiers available among the SLE birth certificates to simulate what the confidence intervals might look like were we able to account for covariance in both the exposed (SLE births) and unexposed (general population births). To maintain an appropriate sample size for the simulations, we did not split up SLE births by timing in relation to diagnosis.

First, we randomly selected a woman with SLE with at least one preterm birth and deleted all of her births from the SLE sample of births. Next, we ran a regression model comparing the risk of preterm birth among the SLE births to the risk among the general population. We progressively deleted randomly selected SLE mothers with at least one preterm birth until the risk ratio equaled 1. Next, we used this sample of SLE mothers where a number of mothers with the outcome were deleted as a pseudo-unexposed cohort, since it now had the same risk of preterm birth as the general population. Finally, we ran a regression model comparing the risk of preterm birth in the original sample of SLE births to the pseudo-unexposed cohort. Since we now had unique identifiers for both the exposed and pseudo-unexposed cohorts, we ran the analysis first not accounting for the covariance between births to the same mother and then accounting for the covariance using generalized estimating equations. We then compared the widths of the 95% confidence intervals for the two risk ratios (width = upper confidence limit/lower confidence limit). We ran the simulation for 20 trials and plotted the moving average after each trial. The same process was repeated using SGA as the outcome of interest.

The plots of confidence interval widths suggest that if we were able to account for the covariance among births in the general population, the confidence intervals around the generated estimates would be wider, but only slightly. In the case of preterm birth, after 20 trials

the average confidence interval width was 1.68 without accounting for covariance and 1.73 when accounting for covariance, an increase of 3.6%. In the case of SGA birth, the average confidence interval width increased from 1.90 to 1.96 after accounting for covariance, an increase of 3.2%. Overall, these simulations suggest that the impact of not accounting for covariance on our estimated confidence intervals is minimal.

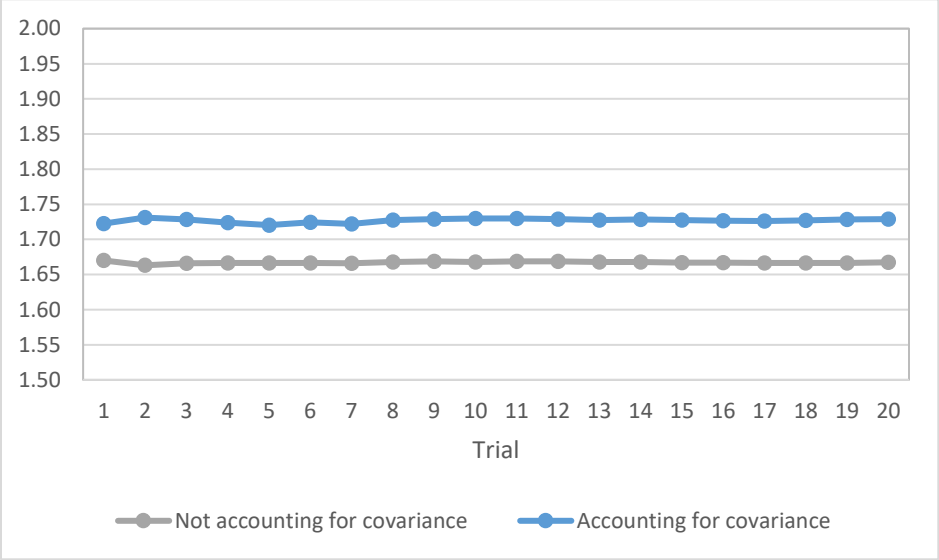

Figure 3-4. Moving average of confidence interval widths after each simulation trial for preterm birth

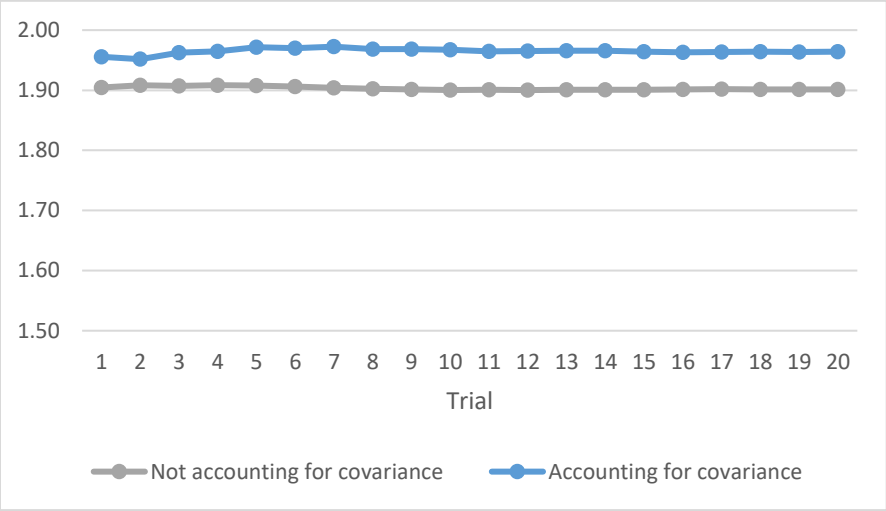

Figure 3-5. Moving average of confidence interval widths after each simulation trial for small-for-gestational age birth

Chapter 4 Cardiovascular Disease After Delivery Among Women with Systemic Lupus Erythematosus

Abstract

Objective: Among women with systemic lupus erythematosus (SLE), pregnancy can be associated with increased disease activity. Separately, women with SLE are at risk for early cardiovascular disease (CVD). We sought to examine the association between parity and CVD among women with SLE.

Methods: Women with SLE identified from the Georgia Lupus Registry were linked with birth certificates. CVD hospitalizations were identified from hospital discharge records and CVD deaths were identified from the National Death Index. We separately compared women who had never been pregnant, women who gave birth only before their SLE diagnosis and women who gave birth both before and after their SLE diagnosis. Extended Cox models were used to estimate hazard ratios for CVD hospitalization or death.

Results: The study sample included 127 women with SLE who had given birth and 141 women who had not. The average length of follow-up was 9.1 years. In unadjusted models, births only before diagnosis and births only after diagnosis were associated with earlier hospitalization or death from CVD after diagnosis, with hazard ratios of 1.53 (95% confidence interval [CI]: 0.85, 2.76) and 1.91 (95% CI: 0.93, 3.94) compared to nulligravid women. Giving birth both before and after diagnosis was also associated with a greater hazard of CVD compared to giving birth before diagnosis only (HR: 2.93, 95% CI: 1.16, 7.36). Results were similar when adjusting for age at diagnosis, race and renal and/or CNS involvement of SLE.

Conclusions: While pregnancy and birth outcomes have improved dramatically for women with SLE, we found that women with SLE are at high risk of cardiovascular disease in the years after delivery. Thus, women with SLE require greater monitoring and coordination of care after delivery.

Introduction

It was once recommended that women with systemic lupus erythematosus (SLE) avoid pregnancy and childbearing. However, with improvements in treatments and knowledge of SLE, it is now understood that with appropriate timing and disease management, women with SLE should not be counseled against pregnancy. Since 2000, both the maternal and fetal death rates among pregnancies to women with SLE have declined dramatically, and women with SLE make up a larger proportion of women giving birth [37]. As part of planning healthy pregnancies, it is recommended that women with SLE wanting to become pregnant have inactive disease for at least six months and establish a treatment regimen that is compatible with pregnancy [2].

Recently, there has been a great deal of attention to the connection between pregnancy and cardiovascular disease (CVD) in the general population, with pregnancy outcomes called “a window to future cardiovascular disease” [53]. Most evidence supports the hypothesis that women with certain pregnancy complications or adverse perinatal outcomes have underlying vascular or metabolic disorders which increases their risk for pregnancy complications and cardiovascular disease later in life [61]. Thus, there is increasing recognition that pregnancy represents an important opportunity to identify women at elevated risk of CVD, with an emphasis on intervening and follow-up for women with adverse birth outcomes [16].

Such interventions may be even more relevant for women with SLE. As an autoimmune disorder that causes inflammation [19, 98], women with SLE already have an increased risk of cardiovascular disease compared with the general population [9, 99]. The incidence of heart failure, coronary heart disease, atherosclerosis and myocardial infarction are higher at younger ages among women with SLE [76], and the established Framingham risk factors do not explain this excess risk [100, 116].

Pregnancy history may provide information beyond traditional risk factors that could be used to identify women with SLE at higher risk for cardiovascular disease. Women with SLE

have a higher risk of adverse perinatal outcomes even before diagnosis of SLE compared to the general population, potentially due to the accumulation of autoantibodies even years before SLE diagnosis [24, 32, 117]. Further, pregnancy itself is often associated with an increased risk of SLE flares, which are periods of higher disease activity, though this association can be modified by medication use [9]. Thus, beyond the relationship between adverse outcomes and cardiovascular disease, pregnancy itself may be predictive of an increased risk of cardiovascular disease among women with SLE. This possibility is suggested by a Taiwanese study that reported a higher risk of heart failure among women with SLE over a mean follow-up of seven years, though the conclusions were based on a small number of events [97]. No studies have examined if giving birth before an SLE diagnosis is predictive of cardiovascular disease risk.

As treatments and prognosis improve for women with SLE, more women with SLE will become pregnant. Of particular concern in the United States, African American women are at greater risk of SLE, adverse birth outcomes, and cardiovascular disease than white women, and yet African American women have been underrepresented in SLE research. If pregnancy is associated with cardiovascular disease among women with SLE, then pregnancy history could be used to help identify the women at greatest risk of cardiovascular disease. In this analysis, we will examine whether women with SLE who gave birth, before or after their SLE diagnosis, are at a greater risk of later hospitalization for CVD or death due to CVD compared to women with SLE who never gave birth in a lupus registry with a high representation of African American women. We hypothesize that women with SLE who gave birth will have an increased hazard of later CVD compared with women with SLE who never gave birth.

Methods

Study Population

The Georgia Lupus Registry (GLR) is a population-based registry of incident and prevalent cases of SLE occurring in Fulton and DeKalb counties in Georgia from 2002 – 2004. The methodology of the GLR has been described previously [3]. Briefly, cases were identified from hospitals, rheumatology, nephrology and dermatology clinics in and around the catchment area. Administrative databases were also queried retrospectively. To be considered a case, individuals had to either meet ≥ 4 of the revised American College of Rheumatology (ACR) Criteria or 3 of the ACR criteria and a diagnosis of SLE by the individual's board-certified rheumatologist documented in the medical record [3]. This analysis is restricted to the female participants in the GLR.

In 2015, the GLR was linked with Georgia birth certificates from 1994 – 2013 on which participants had been identified as the mother on the birth certificate. The GLR was also linked with Georgia inpatient hospital discharge records occurring from 2000 – 2013. Both linkages were performed by the Georgia Department of Public Health using a multi-stage matching algorithm and combinations of identifying keys. The GLR was also linked with the National Death Index (NDI) to identify deaths that had occurred through 2013. NDI records contain up to 20 multiple causes of death.

Cohort Definition

The sample of unique women in GLR was first restricted to women who had been of reproductive age (15 – 44) at some point between 1994 – 2013. We then further restricted the sample to women who had been diagnosed in 2000 or later, as the available hospital discharge data linkage begins in 2000. The cohort of women who gave birth were identified by their linkage to birth certificates. In order to compare the cohort of women who had given birth to a cohort that truly had not given birth, we used all available information to exclude women who had any evidence of pregnancy from the group of women who did not link to birth certificates. Additional variables available in the GLR that were abstracted from medical records document the number of pregnancies, the number of miscarriages and the number of premature births that

women have experienced. We excluded women with any documented history of pregnancy, miscarriage or premature birth from the nulliparous group of women even if they did not link to a birth certificate. This in effect created a comparison group that was nulligravid (never pregnant) rather than nulliparous (never gave birth).

Outcome Definition

Georgia inpatient hospital discharge records were identified and linked to participants in the GLR. The discharge records contain information on admission and discharge date, discharge disposition, principal diagnosis and up to 9 secondary diagnoses. The diagnoses were identified by International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) codes. Based on a literature review of cardiovascular events occurring postpartum, we selected codes to identify coronary heart disease, cerebrovascular disease and congestive heart failure (Appendix Table 1). Deaths were attributed to cardiovascular causes if the NDI record contained ICD-10 codes for coronary heart disease, cerebrovascular disease or heart failure (Appendix Table 1). Women were considered to have the outcome of interest if they had a hospitalization with ICD-9 codes for cardiovascular disease or had a death record with ICD-10 codes for cardiovascular disease.

Covariates

Women were classified by race into 3 groups (African American, White or Other Race) and age at diagnosis (less than 20 years old, 20-29 years old, 30-39 years old, 40 years old or older). An important consideration for this analysis is that women may choose to or choose not to become pregnant for several reasons. Women with more severe SLE may be less likely to choose to become pregnant or less likely to be able to become pregnant. Women with more severe SLE are also more likely to develop cardiovascular disease. To address the issue of SLE severity being a potential confounder, we also included central nervous system and renal manifestations of SLE as captured in the medical record by the time of data extraction. Central nervous system involvement includes psychosis and/or seizures, while renal system

involvement includes a history of lupus nephritis, dialysis and/or kidney transplantation. Central nervous involvement or renal system involvement are both considered indicators of more severe SLE disease and are also associated with cardiovascular disease among people with SLE [71].

Statistical Analysis

We used frequencies and percentages to compare women who had given birth to those who were nulligravid. Extended Cox models were used to compare the hazard of hospitalization or death associated with cardiovascular disease among women who had given birth to those who had never been pregnant. Women were followed from the time of their SLE diagnosis until their first hospitalization attributable to cardiovascular disease or death attributable to cardiovascular disease. Women were censored if they died and the death could not be attributed to cardiovascular causes, or they did not experience the outcome by the end of 2013. Giving birth prior to diagnosis was coded as binary yes/no. Extended Cox models allowed for births after diagnosis to be treated as a time-varying exposure. Women were classified as not having given birth after diagnosis until the date of the birth after their diagnosis, at which point their classification status changed. Estimated hazard ratios and 95% confidence intervals were obtained from the extended Cox models. We first ran unadjusted models, followed by models adjusted for age, race and the severity indicators of central nervous system involvement or renal system involvement. We made three separate comparisons in order to compare like groups. First, we compared women who gave birth only before their SLE diagnosis to nulligravid women. This was in effect a traditional Cox proportional hazards regression model since there was no changing exposure status. This model generated an estimate for the effect of giving birth before diagnosis. Next, we compared women who gave birth only after diagnosis to nulligravid women to estimate the effect of giving birth only after diagnosis. We compared women who gave birth both before and after diagnosis to women who gave birth only before diagnosis to estimate the effect of giving birth after diagnosis among women with SLE who gave birth before their SLE diagnosis. Finally, because death from a non-cardiovascular cause is a

competing event that could potentially bias our estimated hazard ratios, we conducted an additional analysis using Fine-Gray models [118]. The Fine-Gray subdistribution hazard models also allow for time-varying exposures to be included [119]. All analyses were conducted using SAS 9.4 (Cary, N.C.).

Results

We identified 1690 women with SLE from the Georgia Lupus Registry. The sample size was reduced to 637 women when we restricted to women who had been diagnosed after 2000, and further to 524 when we restricted to women of reproductive age during the study period. One-hundred twenty-nine women linked to birth certificates, while 395 did not. After excluding women who had any evidence of prior pregnancies from the group that did not link to birth certificates and women who had cardiovascular-related hospitalizations prior to their diagnosis of SLE, the final study sample included 127 women who had given birth and 141 nulligravid women (Figure 1).

The majority of the study participants were African American, and women who gave birth were more likely to be African American (74.6%) compared to women who did not give birth (66.7%). Slightly higher proportions of the nulligravid women had renal manifestations (27.0%) or central nervous system (12.1%) involvement of SLE compared to parous women (23.6%; 9.5%).

Parous women were a median of 27 years old at the time of their SLE diagnosis (Interquartile Range [IQR]: 22-35) which was similar to nulligravid women who were also a median of 27 years old at the time of their diagnosis (IQR: 18-38). Women who were nulligravid were more likely to be diagnosed at age 40 or older compared to parous women (23.4% compared to 9.5%) and also more likely to be diagnosed before 20 years of age compared to parous women (29.1% vs. 11%). Among women who gave birth, 61.4% (78 women) gave birth only before their SLE diagnosis, 26.0% (33 women) gave birth only after their SLE diagnosis and 12.6% (16 women) gave birth both before and after their SLE diagnosis. When broken

down by timing of first birth, women who gave birth only before their diagnosis were older at their time of diagnosis (32 years, IQR: 24-38) compared to women who had any births after their diagnosis (23 years, IQR: 19.5-27).

Twenty-five women who gave birth (19.7%) and 20 women who did not give birth (14.2%) were hospitalized for CVD or died from CVD after diagnosis. Among African American women, 21.2% were hospitalized or died due to CVD, compared with 7.1% of white women. The median time from SLE diagnosis to CVD hospitalization or death among nulligravid women was 4.0 years (IQR: 1.9-5.9) and among all parous women was 3.6 years (IQR: 1.7-6.7) (Figure 2). Among women who gave birth only before diagnosis, it was 3.0 years (IQR: 0.5-4.4) and among those who gave birth at all after diagnosis, it was 6.1 years (IQR: 3.4-9.3). Among nulligravid women, 65% of CVD hospitalizations and deaths occurred within 5 years of SLE diagnosis. Among women who gave birth only before diagnosis, 87% of CVD hospitalizations and deaths occurred within 5 years of SLE diagnosis, while this proportion is 30% among women who gave birth at all after diagnosis. The most common indicator for CVD hospitalization were ICD codes for heart failure, which were present on 67% of first CVD hospitalizations. Only one woman had a CVD death without a prior CVD hospitalization. Overall, 20.5% (26) of women who had given birth and 19.9% (28) of women who had not given birth died during the follow-up period, with 3 deaths to women who had given birth and 3 deaths to women who had not given birth listing CVD as a cause of death (Appendix Table 2).

In unadjusted models, births only before diagnosis and births only after diagnosis were associated with death or hospitalization for CVD after diagnosis, with hazard ratios of 1.60 (95% confidence interval [CI]: 0.88, 2.90) and 1.70 (95% CI: 0.81, 3.59) (Table 2). The hazard of CVD hospitalization among women who gave birth both before and after diagnosis was almost three times the hazard compared to women who had given birth only before diagnosis (HR: 2.73, 95% CI: 1.04, 7.15), though this estimate had a wide confidence interval. In subsequent models, we controlled for age at diagnosis (<20, 20-29, 30-39, ≥40), race (African American, White, Other

Races) and renal and/or CNS involvement of SLE. The trends remained similar across the models. Hazard ratios changed only slightly when using the Fine-Gray subdistribution hazards model (Appendix Table 3).

Discussion

Overall, our results suggest that women with SLE who had given birth had a greater hazard of hospitalization for cardiovascular disease than women who had never been pregnant. It is important to highlight that even women who gave birth only before their SLE diagnosis (i.e. before any lupus-specific interventions could take place) had a slightly greater hazard of CVD compared to women with SLE who never gave birth. It is now known that with proper timing and disease management, women with SLE can have healthy pregnancies and deliveries. However, far less attention has been paid to the postpartum period among women with SLE. The 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases contains no discussion of postpartum disease management beyond what medications are compatible with breastfeeding [120]. Traditional cardiovascular risk factors, such as high cholesterol, diabetes and hypertension, are not uncommon among women with SLE, but these factors fail to account for the substantially higher risk of CVD among women with SLE [84, 100, 101]. Young women with SLE in general do not present with the classic symptoms of CVD compared to older women or men [102]. Thus, pregnancy may be an important factor to consider in the cardiovascular health of women with SLE.

Several studies suggest that adverse pregnancy outcomes are associated with later cardiovascular disease among women with SLE as with the general population [10, 15, 121]. In addition, women with SLE are reported to be more likely to have cardiovascular disease after delivery compared to women without SLE [54]. However, only one other study of women with SLE has examined pregnancy and childbirth as potential exposures that may increase the risk

of cardiovascular disease [97]. It was conducted in a Taiwanese population and included 149 women with SLE who gave birth and 446 women with SLE without pregnancy over a mean follow-up period of seven years. This study found no differences overall in major adverse cardiovascular events between women with SLE who had and who had not given birth. However, it did report an association, albeit imprecise, between giving birth and heart failure among with women with SLE (OR: 5.4, 95% CI: 1.4, 21.7). In our study, heart failure was the most common indicator of a CVD hospitalization among both parous and nulligravid women with SLE.

Among women with SLE, pregnancy & childbirth, both immediately before and after SLE diagnosis, might be stressors that increases inflammation and therefore risk for cardiovascular disease later in life. The largest and most recent study of the risk of SLE flares during pregnancy found that the risk of flares increases both during pregnancy and 3 months postpartum compared to women with SLE who have not been pregnant, suggesting that pregnancy may be a period of heightened disease activity [9]. This association was modified by use of hydroxychloroquine (HCQ), where women receiving HCQ were not at an increased risk for flares during pregnancy, and it is possible that flares may occur when women stop medication during pregnancy. HCQ is considered safe and is even recommended for use during pregnancy to control SLE disease activity. However, research suggests that HCQ adherence may be low [122]. A large study of Medicaid claims data places nonadherence at 79% among all patients with SLE [123]. While use of HCQ during pregnancy has increased, it still remains low, with an estimate of less than 40% of pregnant women with SLE taking HCQ in 2015 [124]. Monitoring HCQ adherence may be a means to improve cardiovascular outcomes among women with SLE. Furthermore, the effects of weight gain and increased cardiac output experienced by women during pregnancy have not been examined in women with SLE. These factors could also contribute to increased risk for cardiovascular disease after delivery.

Recent research suggests that rheumatologists are somewhat uncomfortable discussing reproductive goals with their patients, due to pregnancies to women with SLE invariably being classified as “high risk” [125, 126]. Nevertheless, SLE itself is not a contraindication to pregnancy. In a pilot study of women with SLE, we found that nearly all participants with SLE wanted at least one child, and women with SLE desired to raise a comparable number of children as women without SLE [127]. Women with SLE want to have children, and in many cases, can have healthy pregnancies and deliveries. In addition to establishing a treatment regimen compatible with pregnancy and ensuring medication adherence, coordination of care between rheumatologists, cardiologists, and obstetrician-gynecologists can help women to plan their pregnancies and can appropriately monitor women for cardiovascular complications. Fragmentation of care is associated with poorer outcomes in people with SLE [128, 129] and rheumatologists recognize the advantages of coordinating care with other physicians for SLE patients [125]. Further, pregnancy generally is a time when women are highly motivated to change health behaviors to improve their own health [130, 131]. Rather than avoiding discussions of reproductive health among women with SLE, clinicians should encourage their patients in an open dialogue about their reproductive goals and how they relate to their health before and after pregnancy.

Our analysis has several important limitations that should be noted. First, our sample size was relatively small, especially when broken down by timing of birth in relation to diagnosis among parous women with SLE which leads to some imprecise estimates. As African American women are at higher risk of SLE and cardiovascular disease compared to white women, it would have been ideal to conduct analyses stratified on race, but our sample size was too small. In our data a substantially greater proportion of African American women were hospitalized or died from CVD compared with white women. Our analysis relied on the linkage of several administrative databases – births, deaths and inpatient hospitalization records. There is the possibility that these linkages may be incomplete or may not capture accurate information

compared to medical records. Deaths were identified through the National Death Index, which does not depend on the deaths occurring in Georgia. According to the NDI, 95% of deaths to GLR participants occurred in Georgia, suggesting that this is not a highly mobile population. It is likely that few births or hospitalizations were missed due to the them occurring out of state. For CVD, inpatient claims data have high positive predictive values [132-134], so it is likely that most inpatient hospitalizations that we captured were true cases. In addition, we excluded a large number of women who had some evidence of pregnancy, but did not link to birth certificates. We could not include them in our analyses because we did not know the outcome of these pregnancies, nor the timing of any live births. These women were generally older at the time of their diagnosis compared to our study population, and had a slightly elevated hazard of CVD hospitalization or death compared with the nulligravid women included in our study. It is likely that this excluded group is a mix of women who gave birth prior to the beginning of our linkage period and women with pregnancies not resulting in live birth. We also only compared women who had a live birth to women who had never been pregnant; women who had pregnancies that were electively or spontaneously terminated are not included. Finally, in using administrative linkages we had limited covariates that we could adjust for as confounders. Insurance status at the time of diagnosis was only available for 50% of the women, so we did not use it in our multivariable analysis. Ideally, we would have liked to adjust for socioeconomic status, as it is both associated with choosing to become pregnant and cardiovascular disease. In addition, we did not have information on medication use. Certain medications, such as cyclophosphamide, are contraindications to pregnancy and also associated with disease severity [2]. As previously mentioned, hydroxychloroquine is recommended in pregnancy to reduce flares and control SLE disease activity.

While pregnancy and birth outcomes have improved dramatically for women with SLE, we found that women with SLE may be at risk of earlier cardiovascular disease after childbirth. Women with SLE need greater monitoring and coordination of care after delivery than women

without SLE. Much of the current research is limited by small sample sizes and single-center populations [135]. The European League Against Rheumatism recently published recommendations for a core data set for pregnancy registries in rheumatology to facilitate analyses and collaborations across registries [136]. While postpartum health is not yet included in the recommended core data set, such registries could aid in linkages and postpartum data collection, which in turn would aid in addressing long term health outcomes. As treatments and the prognosis for women with SLE improve, more women with SLE will become pregnant and have children. While perinatal and immediate maternal outcomes have shown great improvement over time, understanding the relationship between pregnancy and CVD provides the opportunity to identify the women at highest risk and develop interventions to mitigate these risks. Pregnancy is a window to future health is true for all women, but particularly those with underlying conditions such as lupus.

Tables and Figures

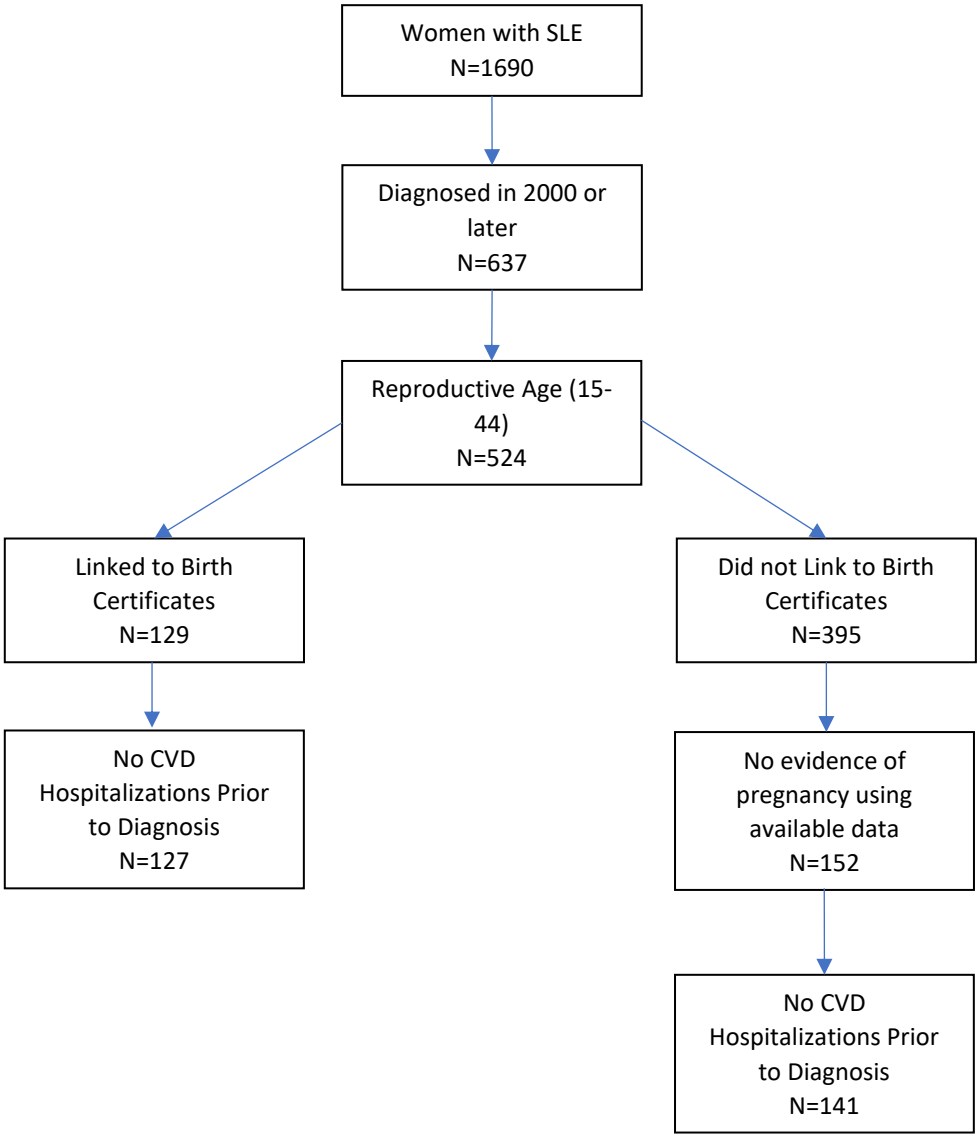

Figure 4-1. Flowchart of exclusion criteria

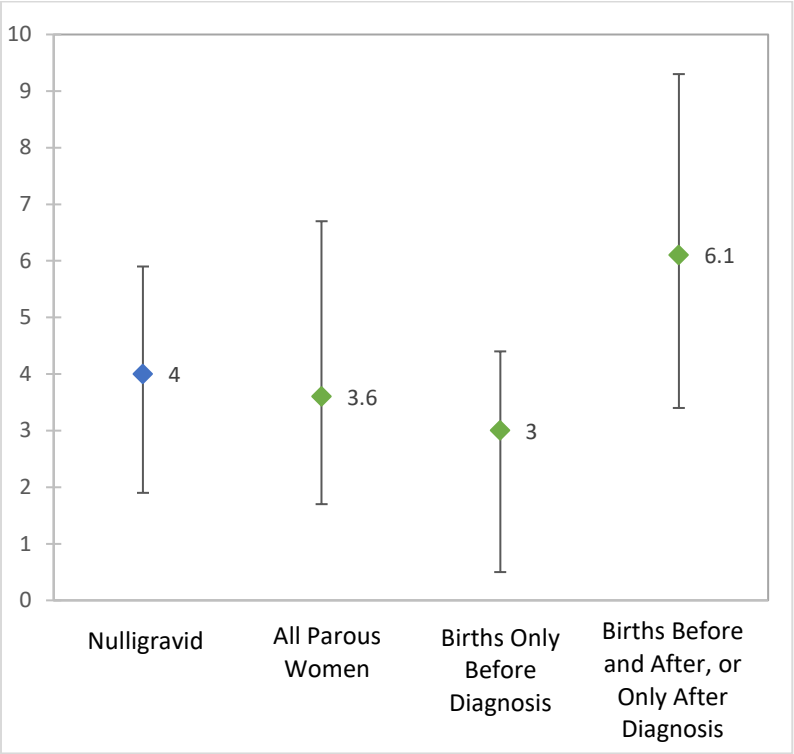

Figure 4-2. Time to CVD hospitalization or CVD death after SLE diagnosis in years (interquartile range)

Table 4-1. Participant characteristics

	Parous (N=127)	Nulligravid (N=141)
Age at Diagnosis		
<20	14 (11.0)	41 (29.1)
20-29	62 (48.8)	35 (24.8)
30-39	39 (30.7)	32 (22.7)
40+	12 (9.5)	33 (23.4)
Race		
African American	95 (74.8)	94 (66.7)
White	28 (22.1)	42 (29.8)
Other	4 (3.2)	5 (3.6)
SLE Severity		
Central Nervous System Manifestations	12 (9.5)	17 (12.1)
Renal Manifestations	30 (23.6)	38 (27.0)
Birth Timing		
Before diagnosis	78 (61.4)	
After diagnosis	33 (26.0)	
Before and After diagnosis	16 (12.6)	

Table 4-2. Estimated hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted for Age HR (95% CI)	…and Race HR (95% CI)	…and CNS, Renal Involvement HR (95% CI)
Births Before vs. Nulligravid	1.53 (0.85, 2.76)	1.92 (1.02, 3.61)	1.74 (0.92, 3.32)	1.60 (0.81, 3.13)
Births After vs. Nulligravid	1.91 (0.93, 3.94)	1.57 (0.73, 3.36)	1.46 (0.67, 3.20)	1.74 (0.77, 3.91)
Births Before and After vs. Births Before	2.93 (1.16, 7.36)	3.01 (1.22, 7.42)	2.55 (1.00, 6.48)	2.78 (1.10, 7.02)

Appendix: Additional Tables

Table 4-3. ICD-9 and ICD-10 codes

	Cardiovascular Disease Identified on Hospital Discharge Records	Cardiovascular Death Identified on the National Death Index Records
Cardiovascular Disease	**ICD-9 Codes**	**ICD-10 Codes**
Coronary Heart Disease	410 – 414, 429.1, 429.2, 429.9, V45.81, V45.82	I20 – I25
Cerebrovascular Disease	431 - 438	160 – I67, G45
Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428	I50, I51.3, I51.9

Table 4-4. Study population deaths

	Parous (N=127)	Nulligravid (N=141)
Died	26 (20.5%)	28 (19.9%)
Median Age at Death (IQR)	32.5 (28.0-38.0)	32.0 (25.0-37.5)
Median Time after Diagnosis to Death in Years (IQR)	6.7 (3.6-9.5)	8.1 (3.5-10.3)

Table 4-5. Estimated hazard ratios using Fine & Gray methods

Model	Unadjusted HR (95% CI)	Adjusted for Age HR (95% CI)	…and Race HR (95% CI)	…and CNS, Renal Involvement HR (95% CI)
Births Before vs. Nulligravid	1.50 (0.84, 2.70)	1.81 (0.99, 3.31)	1.62 (0.87, 3.00)	1.52 (0.80, 2.89)
Births After vs. Nulligravid	2.04 (0.99, 4.22)	1.75 (0.82, 3.75)	1.68 (0.77, 3.66)	1.99 (0.88, 4.47)
Births Before and After vs. Births Before	3.07 (1.21, 7.78)	3.17 (1.27, 7.92)	2.72 (1.05, 7.04)	3.02 (1.17, 7.81)

Chapter 5 Blood Pressure, Carotid Intima Media Thickness, Distensibility and Parity Among African American Women with Systemic Lupus Erythematosus

Abstract

Objective: Some evidence suggests that parity vs. nulliparity is associated with future cardiovascular disease among women with systemic lupus erythematosus (SLE). We sought to examine the association between parity and subclinical measures of cardiovascular health. As women with SLE experience CVD that is not explained by traditional risk factors, we also sought to examine if this association is stronger among African American women with SLE than African American women without SLE.

Methods: African American women with SLE ages 22 – 50 were enrolled from a longitudinal cohort of patients with validated SLE (n=201). A group of African American women without SLE from the same geographic area was enrolled for comparison (n=202). All participants were premenopausal. Women completed structured questionnaires, had their blood pressure measured and carotid artery ultrasounds performed at study visits. Outcomes of interest included systolic and diastolic blood pressure (SBP, DBP), cross-sectional common carotid artery (CCA) distensibility and average carotid IMT, carotid bulb IMT and CCA IMT.

Results: Approximately 70% of each group was parous. Parous women with and without SLE had a similar average age (37.7 and 38.4), with nulliparous women an average of 5 years younger (32.3 and 33.6). After adjusting for demographic and cardiometabolic factors, measures of blood pressure and carotid IMT were not associated with parity among women with SLE, but parous women with SLE had lower distensibility compared with nulliparous women with SLE. Parity was associated with higher SBP and DBP among women without SLE.

Conclusions: Overall, our findings suggest that parity is not associated with blood pressure and IMT among women with SLE, but distensibility is lower among parous women with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is diagnosed in women nine times as often as men [3, 6, 7]. African American women have 3 times the risk of SLE compared with white women [3, 6, 7]. Women with SLE are at greater risk of cardiovascular disease earlier than women without SLE and the disparity is much more pronounced before age 50 [78, 80, 81]. Compared to white women with SLE, African American women with SLE are especially vulnerable to early cardiovascular disease and death [8]. Traditional cardiovascular risk factors fail to account for the substantially higher risk of CVD among women with SLE [84, 100, 101].

In the general population, there is recognition that adverse pregnancy outcomes are a harbinger of later cardiovascular disease, with the risk of maternal CVD 1.5 – 2.0 times greater among women who have experienced adverse birth outcomes [53, 62, 66, 137]. Most evidence tends to support the hypothesis that adverse birth outcomes and pregnancy complications are associated with later cardiovascular disease in the general population because of a common cause; in other words, pregnancy complications and later cardiovascular disease are indicative of underlying vascular health [61]. As in the general population, adverse perinatal outcomes are associated with cardiovascular disease among women with SLE [10]. However, women with SLE are already susceptible to vascular and organ damage [19, 98], and compared to the general population, women with SLE are more likely to develop cardiovascular disease after delivery [54]. Thus, in these women, pregnancy itself may act as a stressor that increases their later risk of cardiovascular disease. Two studies also examined cardiovascular disease after childbirth, comparing parous and nulliparous women with SLE. These studies found that cardiovascular disease, in particular, heart failure, may be more common among parous women with SLE, compared to nulliparous women [97, 138]. Thus, pregnancy may be an important factor to consider in the cardiovascular health of women with SLE.

Elevated blood pressure and atherosclerosis are associated with cardiovascular events including myocardial infarction and cerebrovascular accidents among women with SLE [70, 71]. Research on distensibility in SLE populations is limited, but in the general population lower distensibility is also associated with cardiovascular events [139]. People with SLE have been shown to have greater intima media thickness than people without SLE, and also have more than two times the risk of hypertension [83, 84]. Arterial stiffness, measured by reduced distensibility, has also been shown to be higher among people with SLE [140]. Both IMT and distensibility have not been examined specifically among African American women with SLE. To our knowledge, no studies have examined if women with SLE are more likely to have adverse subclinical markers of cardiovascular health after pregnancy. In the general population, adverse pregnancy outcomes are associated with elevated blood pressure and markers of atherosclerosis later in life [12, 13], while distensibility is lower among women with parity greater than 2 [68]. If blood pressure, atherosclerosis and distensibility are associated with childbirth among women with SLE, parity may provide and easy to measure way to identify women at risk for later CVD and an early opportunity to intervene.

It is especially important to discern the relationship between subclinical CVD and pregnancy among African American women with SLE. African American women represent the racial group at the greatest risk of SLE in the United States, yet they are underrepresented in studies of SLE, particularly in pregnancy-related research [3]. African American women with SLE experience a higher incidence of cardiovascular disease at younger ages than white women [8]. The intersection of SLE, childbirth and cardiovascular health among African American women has not been examined, and is unique from other women. In this analysis we will examine whether there is an association between parity and blood pressure, carotid intima media thickness and distensibility among African American women with SLE. As women with SLE have a higher risk of cardiovascular disease than is explained by traditional risk factors, we

will identify whether this association is unique or stronger among women with SLE by also conducting the same analyses among a group of comparison women without SLE.

Methods

Study Population

We used data from Vascular Aging, Inflammation, and STress in African-American Women's Health Research Study (VISTA), a study that examined whether the specific stressors experienced by African American women contribute to atherosclerotic progression among African American women with SLE. The study recruited African American women ages 22 – 50 with SLE from the Georgians Organized Against Lupus (GOAL) Cohort. GOAL is a longitudinal cohort of individuals with SLE that originally recruited from the Georgia Lupus Registry [17]. Women with SLE had to either meet ≥ 4 of the revised American College of Rheumatology (ACR) Criteria or 3 of the ACR criteria and a diagnosis of SLE by the individual's board-certified rheumatologist documented in the medical record [3]. African American women without SLE were recruited from marketing lists to reflect the geographic distribution of women with SLE recruited from GOAL. All women self-identified as African American, were premenopausal and did not have a history of diabetes, clinical CVD (a history of myocardial infarction, symptoms of angina, intermittent claudication, cerebral ischemia or revascularization) or end stage renal disease at the time of study enrollment. Women without SLE enrolled into the comparison group were also free of any other autoimmune or chronic inflammatory diseases. has collected participant data at baseline, with ongoing visits scheduled for 12 months and 24 months. This analysis only examines participant data collected at baseline.

Study Procedures

Clinic Visit

Participants in the VISTA study attended a clinic visit at one of two locations at Emory University. Participants completed an interviewer-administered questionnaire on demographics, reproductive and health history, behaviors and experiences of stress and support. Participants

had their height, weight and blood pressures measured by trained study staff. At this visit, participants also had a carotid ultrasound assessment. All participants provided written informed consent. All study procedures were approved by the Institutional Review Board of Emory University.

Ultrasound Scan

Carotid intima media thickness and distensibility was assessed by B-mode ultrasonography using standard protocols [141]. Images of the near and far walls of the distal common carotid artery, far wall of the bulb, and first centimeter of the far wall of the internal carotid artery were obtained from the left and right carotid artery. IMT measures were obtained by electronically tracing and measuring the distance between the lumen-intima and the media-adventitia interfaces of the near and far walls of the common carotid artery. Average IMT was the mean value of images averaged across sites. The mean common carotid artery (CCA) measure was assessed across 3 angles. Ultrasound images were read at the University of Pittsburgh Ultrasound Research Lab.

Exposure

The exposure of interest was a history of giving birth (parous vs. nulliparous) among women with SLE and women without SLE. As part of the administered questionnaire, women self-reported the number of times they had given birth and the ages at which their first birth and last (most recent) birth occurred. Using this information, among women with SLE, we could determine if births occurred only before, only after or both before and after the age at which they were diagnosed with SLE. Women were also asked if they had experienced preeclampsia during any of their pregnancies.

Outcomes

Systolic and diastolic blood pressure were treated as continuous values for each participant. Blood pressure and mean arterial pressure were measured in mm Hg. Average IMT, mean bulb IMT and mean CCA IMT were examined for each participant. IMT measurements

were treated as continuous variables and measured in millimeters. Mean common carotid artery cross-sectional distensibility was calculated as (∆A) / (PP*A), where ∆A is the stroke-change in the lumen area, PP is the difference between systolic and diastolic blood pressure and A is the diastolic lumen area [142].

Covariates

Age at the time of the clinic visit, highest level of education completed and Medicaid use in the past year were all collected as part of the questionnaire. Women also reported if they had ever been told by a doctor that they had hypertension or high cholesterol. Women reported the number of minutes they spent on in various physical activities during a typical week. The minutes of activity spent on each activity were multiplied by the appropriate metabolic equivalent, and then converted to MET-hours/week [143]. We used the summary variable of intentional exercise, which summed the MET-hours/week spent playing sports, dancing, walking for exercise or participating in conditioning activities [144]. Body mass index was calculated using participants' measured weight and height and categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to less than 25 kg/m^2), overweight (25 kg/m^2 to less than 30 kg/m^2) and obese (more than 30 kg/m^2). Women were also asked if they had ever been a regular smoker, defined as smoking at least 20 cigarettes during a typical week. Regular smoking was defined as current, former or never.

Analysis

There were four exposure categories of interest: parous women with SLE, nulliparous women with SLE, parous women without SLE and nulliparous women without SLE. Frequencies and percentages were used to compare the distribution of demographic and cardiometabolic/behavioral characteristics across these four exposure groups. In multivariable linear models, SLE and parity (parous vs. nulliparous) were included as exposure variables, along with an interaction term for SLE*parity. Estimated beta coefficients were then generated separately for women with SLE and women without SLE for the association between parity and

each of the outcome variables of interest. We examined these associations using models that sequentially adjusted for different covariates. Model 1 adjusted for age only. Model 2 adjusted for age, education and Medicaid use in the past year. Model 3 adjusted for age, education, Medicaid use in the past year, intentional exercise, regular smoking and BMI. In models including average, bulb or CCA IMT or distensibility as the outcome, model 3 also adjusted for systolic blood pressure.

Finally, we ran three sensitivity analyses using the fully adjusted models for each outcome of interest. Model 4 excluded women who had ever been diagnosed with hypertension, as hypertension medication may affect observed values of IMT [13]. Model 5 excluded women who had given birth and had a history of preeclampsia. Lastly, to account for the possibility of confounding by indication where women with severe SLE may be less likely to get pregnant and be at greater risk of SLE. In model 6, we only included parous women who only gave birth prior to their SLE diagnosis. All analyses were conducted in SAS 9.4 (Cary, NC).

Results

Our analysis included 201 African American women with SLE and 202 African American women without SLE. Approximately 70% of each group were parous (Table 1). Parous women with and without SLE had a similar average age (37.7 and 38.4), and nulliparous women were an average of 5 years younger than their parous counterparts (32.3 and 33.6). Nearly 90% of nulliparous women with SLE were diagnosed in their twenties, compared to 63.5% of parous women with SLE. A noticeably larger proportion of parous women with SLE had a high school education or less (47.1%, compared to ~ 30% among all other groups) and had used Medicaid in the previous year to pay for health care (45.7%, compared to 30.2% among nulliparous women with SLE, 25.0% among parous women without SLE and 6.6% among nulliparous women without SLE). Among parous women, 23.9% of women with SLE had a history of preeclampsia, compared with 8.6% of women without SLE. Age at first birth was similar between parous women with SLE and parous women without SLE (21.0 vs. 22.8). Women with

SLE in general were more likely to have been diagnosed by a healthcare provider with either hypertension or high cholesterol (Table 2). In all groups, women were most commonly obese. The number of MET-hours of intentional exercise performed each week varied widely within each group, and parous women with SLE had the lowest median value. The vast majority of women in each group were never smokers.

Mean systolic and diastolic blood pressure was very similar among parous women with SLE, nulliparous women with SLE and parous women without SLE, while nulliparous women without SLE had noticeably lower values (Table 3). Average IMT was similar across groups and identical among parous women (0.57 mm) and nulliparous women (0.55 mm). Mean bulb IMT and mean CCA IMT showed similar patterns. Mean CCA distensibility was 4.98 1/mmHg * 10^{-3} among nulliparous women with SLE and without SLE. Parous women with SLE had a slightly lower mean CCA distensibility (4.14 1/mmHg * 10^{-3}) than parous women without SLE (4.23 1/mmHg * 10^{-3}).

In models examining the association between blood pressure measures and parity, SBP and DBP were not associated with parity among women with SLE (Table 4). Among women without SLE, parous women had SBP and DBP values that were on average 4 - 5 points higher than for nulliparous women. These differences persisted even after adjusting for age, education, Medicaid use, high cholesterol, BMI, intentional exercise and smoking. Average IMT, mean bulb IMT and mean CCA IMT were not associated with parity among African American women with SLE or without SLE. Associations did not change in adjusted models. Among women with SLE, parous women had lower mean CCA distensibility than nulliparous women after adjusting for age (β=-0.432; 95% confidence interval [CI]: -0.802, -0.063) and this association remained consistent even after adjusting for all factors in model 3. Among women without SLE, there was a weaker association between parity and SLE, with parous women having a mean CCA distensibility that was 0.172 1/mmHg * 10^{-3} less than nulliparous women in fully adjusted models (95% CI: -0.539, 0.195).

In sensitivity analyses that excluded women with hypertension, women with a history of preeclampsia and parous women with SLE who had births after their SLE diagnosis (models 4-6), there was no association between parity and any IMT measures among women with SLE or women without SLE. Among women without SLE, associations between parity and SBP and DBP were attenuated in models that excluded women with hypertension and models that excluded women with a history of preeclampsia. Excluding women with SLE who gave birth after their SLE diagnosis had very little effect on the estimated coefficients among women without SLE. The association between mean CCA distensibility and parity was strengthened among women with SLE when excluding women with diagnosed hypertension (model 4) but attenuated among women without SLE. Among women without SLE, the association between parity and CCA distensibility was attenuated when excluding women with a history of preeclampsia (model 5). Results were largely unchanged when excluding women who gave birth after their SLE diagnosis (model 6).

Discussion

In this analysis of African American women with SLE and African American women without SLE, similar proportions of each group were parous. In crude analyses, blood pressure, measures of IMT and mean CCA distensibility were similar among parous women, regardless of SLE status. Nulliparous women with SLE had slightly higher blood pressure compared to nulliparous women without SLE, though IMT and mean CCA distensibility were similar. When treating SLE as an effect modifier in the association between parity and cardiovascular factors, parity was not associated with blood pressure or IMT among women with SLE. However, parous women with SLE had lower mean CCA distensibility than nulliparous women with SLE, even after adjusting for demographic and cardiometabolic characteristics and behaviors. Overall, our results suggest that blood pressure and/or IMT measurements are not appreciably higher among parous women with SLE, but parity does appear to be associated with mean CCA

distensibility. Measuring arterial stiffness may be a way to identify women with SLE who are at risk of cardiovascular disease after childbirth. Among women without SLE, we found that blood pressure was associated with parity, even after adjustment for demographic and cardiometabolic factors. It is possible that even after adjusting for age, and other cardiometabolic factors, this is reflective of nulliparous women without SLE in general being younger and healthier than parous women without SLE.

It is noteworthy that we only observed significant differences by SLE status for our measures of distensibility, and not IMT or blood pressure. However, there is some support for this in the literature. In a study conducted among Taiwanese women with SLE, there was no association between parity and major adverse cardiovascular events in general, but parous women with SLE were more likely to experience earlier heart failure compared with nulliparous women with SLE [97]. In our own analysis of parity and cardiovascular disease among women with SLE, congestive heart failure was the most common indication for CVD hospitalization [138]. While IMT and blood pressure have been shown to be associated with heart failure [72, 73], arterial stiffness has been more directly implicated in the etiology of heart failure, and may therefore be a more salient predictor of heart failure in our population [74, 145, 146]. The finding that distensibility is associated with parity is valuable as arterial stiffness is modifiable through medication and/or health behaviors [147, 148]. In addition, a study of SLE patients found that reduced SLE disease activity was associated with improvements in arterial stiffness [149]. African American women with SLE are more likely to experience periods of sustained disease activity than white women, and persistently active disease is associated with CVD among people with SLE over a 10-year follow-up [150, 151].

There are several reasons we may not have seen differences in blood pressure or IMT by parity in women with SLE. Our sample was fairly young, with an average age of 38. Differences in CVD health by adverse pregnancy status have been found among women over age 60 [13]. It is possible that our sample was too young for these differences to manifest.

Furthermore, our sample, although large for a study sample of African American women with SLE, may have been too small to detect differences between parous and nulliparous women. Several studies in the general population that did find differences in IMT between women with adverse birth outcomes and women without with an average age that was similar to our study included samples that were more than twice as large as our sample [12, 137, 152]. In addition, a study that found distensibility to be associated with parity greater than 2 in the general population did not find parity associated with intima media thickness, suggesting that arterial stiffening and atherosclerosis have separate distinct associations with parity [68].

Our analysis has several limitations that should be noted. Despite the fact that our study population included a uniquely large sample of African American women with SLE, when stratified by parity, our analytical samples become smaller. It is possible that our sample was too small to detect meaningful differences in blood pressure or IMT among women with SLE. This was also a cross-sectional analysis, with a self-reported history of previous birth. We did not have baseline measures of cardiometabolic or SLE-specific health prior to pregnancy. In addition, mean CCA distensibility was measured using brachial blood pressure, but carotid blood pressure would have been ideal for controlling for the confound effects of blood pressure [153]. While we did conduct a sensitivity analysis that excluded women who became pregnant after their SLE diagnosis, we cannot rule out the possibility that some women may have chosen not to have biological children or could not have biological children based on their underlying health, which would have likely biased our results to the null if there were a true association. Despite the fact that the aim of this study was to examine parous vs. nulliparous women, these are heterogenous groups. Parous women have varying numbers of births and births with different perinatal outcomes. Nulliparous women include women who have never been pregnant and women who were pregnant but did not have a live birth. It is possible that we may have found different results if we examined exposures at a more granular level.

Our analysis is one of the few studies to examine reproductive exposures and subclinical CVD measures specifically among African American women with SLE. We found arterial distensibility to be lower among parous African American women with SLE compared to nulliparous women with SLE. Research in recent years has demonstrated that women with SLE can have healthy pregnancies and deliveries, though these pregnancies and births should be carefully planned and managed [120]. However, young women with SLE remain at high risk of early CVD [8, 78, 80]. Monitoring arterial stiffness among parous women with SLE may be an effective was to identify women at risk of later CVD and intervene early.

Tables

Table 5-1. Participant characteristics

	SLE		No SLE	
	Parous (N=138)	Nulliparous (N=63)	Parous (N=140)	Nulliparous (N=61)
Age at Survey				
19-34	31.2 (43)	65.1 (41)	22.9 (32)	62.3 (38)
35-39	23.2 (32)	9.5 (6)	32.1 (45)	16.4 (10)
40-44	24.6 (34)	15.9 (10)	30.0 (42)	16.4 (10)
45+	21.0 (29)	9.5 (6)	15.0 (21)	4.9 (3)
Education				
High School or Less	47.1 (65)	28.6 (18)	30.0 (42)	26.2 (16)
Some College	16.7 (23)	19.1 (12)	20.0 (28)	13.1 (8)
College	22.5 (31)	49.2 (31)	40.7 (57)	52.5 (32)
Missing	13.8 (19)	3.2 (2)	9.3 (13)	8.2 (5)
Medicaid Past Year	45.7 (63)	30.2 (19)	25.0 (35)	6.6 (4)
Age at SLE Diagnosis				
<20	17.5 (24)	35.5 (22)		
20-29	46.0 (63)	53.2 (33)		
30-39	30.7 (42)	11.3 (7)		
40-50	5.8 (8)	0.0 (0)		
History of Preeclampsia	23.9 (33)		8.6 (12)	
Age at First Birth (Mean, SD)	21.0 (4.6)		22.8 (5.5)	
Time Since Last Birth (Mean, SD)	12.0 (7.6)		9.9 (6.4)	

Table 5-2. Cardiometabolic characteristics/behaviors

	SLE		No SLE	
	Parous (N=138)	Nulliparous (N=63)	Parous (N=140)	Nulliparous (N=61)
Hypertension	58.7 (81)	40.3 (25)	24.3 (34)	11.5 (7)
High Cholesterol	18.1 (25)	14.3 (9)	3.6 (5)	9.8 (6)
BMI				
Underweight	2.2 (3)	1.7 (1)	0.7 (1)	8.2 (5)
Normal weight	23.9 (32)	32.2 (19)	19.0 (26)	26.2 (16)
Overweight	26.1 (35)	30.5 (18)	21.2 (29)	21.3 (13)
Obese	47.8 (64)	35.6 (21)	59.1 (81)	44.3 (27)
Intentional Exercise (MET hr/week) (Median, IQR)	14.4 (0.2, 35.0)	21.8 (5.0, 62.5)	29.0 (10.0, 56.0)	27.9 (10.5, 70.0)
Regular Smoking				
Current	7.3 (10)	6.4 (4)	7.1 (10)	0.0 (0)
Former	10.9 (15)	7.9 (5)	6.4 (9)	3.3 (2)
Never	81.9 (113)	85.7 (54)	86.4 (121)	96.7 (59)

Table 5-3. Measures of blood pressure, carotid intima media thickness and distensibility

	SLE		No SLE	
	Parous (N=138)	Nulliparous (N=63)	Parous (N=140)	Nulliparous (N=61)
Diastolic Blood Pressure (mm/Hg)	82.0 (12.4)	81.0 (11.3)	80.6 (12.4)	75.5 (12.1)
Systolic Blood Pressure (mm/Hg)	120.2 (16.4)	119.0 (15.2)	120.9 (16.4)	114.8 (13.4)
Mean average IMT of 3 segments and 3 angles (mm)	0.57 (0.09)	0.55 (0.07)	0.57 (0.07)	0.55 (0.08)
Mean of average bulb IMT (mm)	0.63 (0.13)	0.60 (0.11)	0.62 (0.12)	0.59 (0.12)
Mean of average CCA IMT (mm)	0.59 (0.07)	0.57 (0.07)	0.60 (0.07)	0.58 (0.08)
Mean CCA cross-sectional distensibility ($1/mmHg * 10^{-3}$)	4.14 (1.22)	4.98 (1.56)	4.23 (1.37)	4.98 (1.32)

Table 5-4. Associations between parity and blood pressure, carotid intima media thickness and distensibility

		SLE (β [95% confidence interval])	No SLE (β [95% confidence interval])
SBP			
	Model 1	-0.45 (-5.24, 4.34)	4.34 (-0.55, 9.23)
	Model 2	-0.30 (-5.37, 4.78)	5.66 (0.55, 10.78)
	Model 3	-1.19 (-6.32, 3.95)	5.34 (0.14, 10.55)
DBP			
	Model 1	0.36 (-3.35, 4.06)	4.37 (0.57, 8.16)
	Model 2	0.09 (-3.86, 4.03)	5.20 (1.23, 9.18)
	Model 3	-0.44 (-4.32, 3.44)	4.06 (0.13, 7.99)
Mean average IMT			
	Model 1	-0.00 (-0.03, 0.02)	-0.006 (-0.03, 0.02)
	Model 2	-0.00 (-0.03, 0.02)	-0.003 (-0.03, 0.02)
	Model 3	0.00 (-0.02, 0.03)	-0.002 (-0.03, 0.02)
Mean of average bulb IMT			
	Model 1	0.00 (-0.04, 0.04)	0.00 (-0.04, 0.04)
	Model 2	0.01 (-0.03, 0.05)	0.00 (-0.04, 0.04)
	Model 3	0.01 (-0.03, 0.06)	0.00 (-0.04, 0.04)
Mean of average CCA IMT			
	Model 1	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)
	Model 2	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)
	Model 3	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Mean CCA cross-sectional distensibility			
	Model 1	-0.432 (-0.802, -0.063)	-0.292 (-0.673, 0.088)
	Model 2	-0.461 (-0.857, -0.065)	-0.361 (-0.763, 0.041)
	Model 3	-0.492 (-0.850, -0.134)	-0.172 (-0.539, 0.195)

Model 1: Adjusted for age at survey

Model 2: Adjusted for age at survey, Medicaid in past year, education

Model 3: Adjusted for age at survey, Medicaid in past year, education, BMI, regular smoking, intentional exercise, high cholesterol (IMT and distensibility models also adjusted for SBP)

Table 5-5. Sensitivity analyses

		SLE (β [95% confidence interval])	No SLE (β [95% confidence interval])
SBP			
	Model 4	-1.44 (-6.92, 4.02)	2.37 (-2.05, 6.79)
	Model 5	-1.43 (-6.65, 3.80)	4.31 (-0.84, 9.45)
	Model 6	1.00 (-5.04, 7.04)	5.85 (0.49, 11.20)
DBP			
	Model 4	-1.61 (-5.90, 2.68)	2.37 (-1.09, 5.83)
	Model 5	-1.14 (-5.05, 2.78)	3.45 (-0.40, 7.30)
	Model 6	0.99 (-3.53, 5.49)	4.51 (0.51, 8.51)
Mean average IMT			
	Model 4	0.00 (-0.03, 0.03)	0.00 (-0.02, 0.03)
	Model 5	0.01 (-0.02, 0.03)	0.00 (-0.03, 0.03)
	Model 6	0.01 (-0.02, 0.04)	-0.01 (-0.03, 0.02)
Mean of average bulb IMT			
	Model 4	0.00 (-0.05, 0.05)	0.00 (-0.03, 0.04)
	Model 5	0.02 (-0.03, 0.06)	0.00 (-0.04, 0.05)
	Model 6	0.02 (-0.02, 0.07)	-0.00 (-0.05, 0.04)
Mean of average CCA IMT			
	Model 4	-0.01 (-0.03, 0.02)	0.00 (-0.02, 0.02)
	Model 5	0.00 (-0.07, 0.03)	-0.01 (-0.03, 0.01)
	Model 6	-0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Mean CCA cross-sectional distensibility			
	Model 4	-0.717 (-1.216, -0.219)	-0.135 (-0.540, 0.270)
	Model 5	-0.527 (-0.904, -0.149)	-0.144 (-0.519, 0.232)
	Model 6	-0.338 (-0.761, 0.085)	-0.204 (-0.582, 0.174)

Model 4: Excluded women with diagnosed hypertension: adjusted for age at survey, Medicaid in past year, education, BMI, regular smoking, intentional exercise, high cholesterol (IMT and distensibility models also adjusted for SBP)
Model 5: Excluded women with history of preeclampsia: adjusted for age at survey, Medicaid in past year, education, BMI, regular smoking, intentional exercise, high cholesterol (IMT and distensibility models also adjusted for SBP)
Model 6: Excluded women with births only after SLE diagnosis: adjusted for age at survey, Medicaid in past year, education, BMI, regular smoking, intentional exercise, high cholesterol (IMT and distensibility models also adjusted for SBP)

Chapter 6 Conclusions, Impact & Future Research

Summary of Findings

Findings from Aim 1

African American are at greater risk of SLE and adverse perinatal outcomes compared to white women, yet few studies specifically examine the risk of adverse perinatal outcomes among African American women with SLE. We compared the risk of preterm birth and small-for-gestational age among African American women with SLE to the risk in the general population of African American women. We also examined the risk of these adverse perinatal outcomes by the timing of birth in relation to SLE diagnosis.

We found that African American women with SLE are at greater risk of preterm birth and small-for-gestational age than the general population, and that this increased risk varies by when the birth occurred in relation to SLE diagnosis. After adjusting for maternal age, education and parity, women were not at risk of giving birth to preterm or small-for-gestational age infants more than three years before their diagnosis compared to the general population. However, within three years before their diagnosis, compared to the general population, African American women with SLE have 1.71 times the risk of preterm birth (95% CI: 1.24, 2.35) and 2.38 times the risk of small-for-gestational age (95% CI: 1.69, 3.36). The relative risk of preterm birth is highest 3 years or more after diagnosis 2.83 (95% CI: 2.36, 3.38) while the relative risk of small-for-gestational age is highest within three years after diagnosis 2.89 (95% CI: 2.03, 4.13) compared to the general population.

These results align with previous studies that suggest a pre-disease state of SLE that may influence perinatal outcomes in the years before SLE is clinically diagnosed. In addition, our results show a greater risk of preterm birth (nearly 40% more than three years after diagnosis) among African American women with SLE than had previously been identified in SLE populations.

Findings from Aim 2

Research has shown that women with SLE are both at risk of cardiovascular disease after experiencing adverse birth outcomes, and at greater risk of cardiovascular disease at younger ages than the general population. Among women with SLE, pregnancy could be a stressor that increases their risk of CVD following delivery. Only one other study, conducted in a Taiwanese population, has examined the risk of cardiovascular disease between nulliparous and parous women with SLE. In our analysis, we examined the risk of hospitalization or death due to cardiovascular disease after delivery in a predominantly African American study population of women with SLE, considering both births before and after SLE diagnosis.

Our results suggest there may be an increased hazard of cardiovascular disease among parous women with SLE compared with nulligravid women with SLE. After adjusting for age, race and renal/central nervous system involvement of SLE, births before diagnosis and births after diagnosis had a slight greater hazard of earlier hospitalization or death from CVD after SLE diagnosis, with hazard ratios of 1.60 (95% CI: 0.81, 3.13) and 1.74 (95% CI: 0.77, 3.91) compared to nulligravid women. Giving birth both before and after diagnosis was also associated with a greater hazard of CVD compared to giving birth before diagnosis only (HR: 2.78, 95% CI: 1.10, 7.02). Although we controlled for severe manifestations of SLE, we expect that SLE disease severity potentially biased our results towards the null. While these results are based on a small sample size, they consistently suggest that parity is associated with cardiovascular disease, even when births occur before diagnosis.

This analysis is the second study to suggest an increased hazard of CVD among parous women compared to nulliparous women with SLE. Although perinatal outcomes have improved drastically for women with SLE, there remains an unmet need to support women with SLE during the postpartum period and beyond. Among women with SLE, who have rates of CVD not explained by traditional risk factors, pregnancy and childbirth history may be even more important to consider than in the general population in assessing cardiovascular risk.

Findings from Aim 3

Following our analysis in Aim 2, we sought to examine if subclinical markers of cardiovascular health, specifically blood pressure, carotid intima media thickness (IMT) and distensibility were associated with parity among African American women with SLE. Since women with SLE are at a uniquely high risk of SLE compared with women without SLE, we also examined if this association was unique or stronger among women with SLE compared with women without SLE.

Contrary to our hypotheses, we did not find blood pressure or IMT to be associated with parity among African American women with SLE. However, among women with SLE common carotid artery distensibility was lower among parous women compared with nulliparous women, and this association remained in sequentially adjusted models. Among African American women without SLE, we did find that blood pressure was higher among parous women compared with nulliparous women.

We found arterial distensibility to be lower among parous African American women with SLE compared to nulliparous women with SLE. Monitoring arterial stiffness may be an effective way to identify parous women with SLE at risk of later CVD.

Strengths and Limitations

Strengths

This dissertation had several strengths that addressed important gaps in the current literature. First, all of the analyses in this dissertation included a study sample of women with SLE drawn the Georgia Lupus Registry (GLR) and the Georgians Organized Against Lupus (GOAL) Cohort. These studies only enroll participants with SLE validated from medical records according to the American College of Rheumatology Criteria [21]. SLE can be a complex and multi-factorial disease and studies have shown that when cases are identified from administrative data using ICD-9-CM codes, the positive predictive value is 60% [46]. This

suggests that a number of cases are incorrectly identified as SLE. In addition, the participants in GLR and GOAL are also 80% African American, reflecting the distribution of SLE in the Atlanta metropolitan area [17]. African American women represent the racial/ethnic group at the greatest risk of SLE in the United States, yet they are underrepresented in studies of SLE, especially studies that relate to reproductive health [3, 6, 7].

Considering parity as a potential exposure in Aims 2 and 3 is one of the most innovative aspects of this dissertation. To date, only one other study has examined childbirth as a risk factor for cardiovascular disease in women with SLE [97]. By including both parous and nulliparous women with SLE in our analyses, we were able to consider parity as a risk factor for CVD in a population that is uniquely vulnerable to CVD.

Finally, in our first two aims, as a result of the linkage to Georgia birth certificates, we were able to consider births both before and after SLE diagnosis. This was important for two reasons: 1) people who will eventually be diagnosed with SLE can have autoimmune antibodies years before they meet the clinical criteria for SLE and 2) people who do meet the clinical criteria for SLE often experience delays in diagnosis [22, 24]. Several studies have demonstrated that women who will eventually be diagnosed with SLE are at risk of adverse perinatal outcomes in the years before their diagnosis [31, 32, 47]. Our findings in Aim 1 supported these results. In Aim 2, we used models with time-varying exposures to examine women who gave birth both before and after their SLE diagnoses and found that women who gave birth before their SLE diagnosis may have an increased hazard of cardiovascular disease compared with nulligravid women. These results suggest that exposures even before a clinical SLE diagnosis should be considered when assessing risks associated with SLE.

Limitations

In addition to the specific limitations pertaining to each individual aim, there are several overarching limitations that are relevant to the dissertation as a whole.

Limitations of administrative data

Aims 1 and 2 relied on linkages to birth certificates and hospital discharge data, which collect variables for administrative, rather than research purposes. Across states, birth certificate variables for gestational age and birthweight tend to show high validity when compared to medical records [154, 155] and for CVD, inpatient claims data have high positive predictive values [132-134]. However, we did not have access to some variables that would have been valuable to control for confounding. For Aims 1 and 2, insurance status would have been useful as a proxy measure of socioeconomic status. In Georgia, maternal receipt of WIC and insurance status were only available on the birth certificate beginning in 2009 which would have rendered our sample size too small to conduct a multivariable analysis for Aim 1. Insurance status at the time of diagnosis was only available for 50% of the women in the GLR for Aim 2. In addition, we did not have information on medication use. Cyclophosphamide is contraindicated in pregnancy and also associated with disease severity, prednisone use is associated with adverse perinatal outcomes and hydroxychloroquine has been shown to reduce the risk of flares in pregnancy [2, 9, 50].

With administrative linkages there is also the possibility that linkages were incomplete. This is especially a concern for Aim 2, where identification of parous and nulliparous women relied on data linkages. According to the National Death Index, 95% of deaths to GLR participants occurred in Georgia. This suggests few births and hospitalizations to women were missed because they occurred out of state. In addition, we excluded a large number of women who had some evidence of pregnancy, but did not link to birth certificates. It is likely that this excluded group is a mix of women who gave birth prior to the beginning of our linkage period and women with pregnancies not resulting in live birth.

Sample size concerns

In Aim 2, our sample size was relatively small, especially when broken down by timing of birth in relation to diagnosis among parous women with SLE. Some of the estimates generated

in Aim 2 were somewhat imprecise, and the overall trend of the estimates that suggest an association between parity and CVD should be highlighted, rather than individual estimates. In Aim 3, when divided by parity, again our analytical samples were relatively small. It is possible that our sample was too small to detect meaningful differences in blood pressure or IMT among women with SLE. In the context of the SLE literature, our study samples were uniquely large, especially in their inclusion of African American women with SLE. The imprecision of our estimates should be weighed against the gaps in the literature that they address.

Limitations in generalizability

Our analyses include an understudied population of African American women with SLE, but this population was identified primarily in the Atlanta metropolitan area. Studies show a strong urban-rural divide in terms of SLE diagnosis timing and outcomes [156]. Our results may not be applicable to or reflect the treatment experiences of women living in regions with limited access to rheumatologists or medical facilities. In addition, Aims 1 and 3 were restricted to African American women with SLE, and the study population in Aim 2 was largely African American and white. Hispanic and Asian women also have a higher risk of SLE compared to white women [3, 4] but our results may not reflect the experiences of Hispanic and Asian women.

Public Health Impact

In this dissertation, we sought to characterize the risks associated with systemic lupus erythematosus, adverse birth outcomes and CVD among women, with particular representation of African American women. We found that risks of adverse perinatal outcomes and CVD among parous women may be elevated among women with SLE before they are diagnosed with SLE. Healthcare providers, especially those in communities of color, should be better educated about SLE, and have a lower threshold to suspect SLE in the peripartum period. As in the general population, pregnancy is both a potential harbinger of later cardiovascular risk and potential point of intervention [61, 157]. Coordination of care between rheumatologists,

cardiologists and obstetrician-gynecologists can help women to plan their pregnancies and can appropriately monitor women for cardiovascular complications. Increasing adherence to hydroxychloroquine during pregnancy, which historically is low, may be a means to improve cardiovascular health during the postpartum period [124, 149].

In our unpublished analysis of a pilot study of African American women in GOAL, we found that having biological children was as important to women with SLE as women without SLE and wanting children did not depend on the severity of their disease. In a separate study, we found that the average number of children desired by African American women with SLE did not differ from women without SLE [127]. Women with SLE want to have children, and in many cases, can have healthy pregnancies and deliveries. However, women with SLE experience a complex interaction of autoimmune, cardiovascular, and reproductive risks, and it is important that all of these risks are considered. Clinicians should encourage their patients in an open dialogue about their reproductive goals and how they relate to their health before and after pregnancy. This is especially true for African American women with SLE, who are at greater risk of adverse perinatal outcomes and early CVD [8, 38, 39]. The quality of interactions with healthcare providers also appears to show a stronger relationship with medication adherence and organ damage among African American SLE patients than white patients [158, 159]. In this dissertation, we provided evidence for the risk of adverse perinatal outcomes before SLE diagnosis among African American women and identified pregnancy as a potential important point of intervention for cardiovascular health among women with SLE.

Future Research

This dissertation has generated several questions to be addressed in future studies. As was also an issue in this dissertation, much of the current research on reproductive health among women with SLE is limited by small sample sizes [135]. Previous studies have either utilized small, center-based samples of SLE patients that may not be representative of all SLE

patients or national administrative databases where SLE is identified by administrative codes, which may not be accurate, and are limited in the questions they can address. The European League Against Rheumatism recently published recommendations for a core data set for pregnancy registries in rheumatology to facilitate analyses and collaborations across registries [136]. While postpartum health is not yet included in the recommended core data set, such registries could aid in linkages and postpartum data collection, which in turn would aid in addressing long term health outcomes.

There continues to be a need for studies of long-term outcomes after delivery among women with SLE. Additional research on the incidence of cardiovascular disease, but also kidney disease, are needed. Three studies examining renal complications after pregnancy in an SLE population found no association, but these we both conducted in non-U.S. populations [93-95]. In the United States, the incidence of end stage renal disease among African American patients with SLE is nearly 4 times that among white patients with SLE and its association with pregnancy has not been studied [160]. Further studies are needed to both conduct our analyses in additional populations and examine other serious morbidities that may follow pregnancy in women with SLE.

Additionally, future studies should examine other components of postpartum cardiovascular health of women with SLE. While we did not find differences in blood pressure or carotid intima media thickness between parous and nulliparous women, other markers of atherosclerosis, in particular arterial plaque, may be more important to consider. It is suggested that plaque is a better predictor than IMT of CVD among people with SLE [161]. In addition, SLE specific-factors may prove to be important factors to consider. African American women with SLE are more likely to experience periods of sustained disease activity than white women, and disease activity is associated with organ damage [99, 150]. Monitoring disease activity during the postpartum period may be a means to identify women at greater risk of cardiovascular disease.

Finally, additional research should examine socioeconomic and psychosocial factors as they relate to pregnancy outcomes and cardiovascular disease. A recent study has suggested that clinical factors, including disease activity and physician visits, do not account for racial disparities in adverse perinatal outcomes among women with SLE, but disparities may be explained by socioeconomic factors [38]. The higher risk of cardiovascular disease among women with SLE remains unexplained by traditional risk factors. In Aim 3, we only found carotid distensibility was associated with parity among women with SLE, but not blood pressure or IMT. Experiences of racism and discrimination are associated with disease activity and disease damage among African American women with SLE [162, 163]. In the general population of African American women, discrimination and other psychosocial stressors are associated with cardiovascular health [164, 165]. The intersection of experiences of life stressors and cardiovascular health among African American women with SLE may provide additional insight in the association between parity and cardiovascular disease, and identify opportunities for intervention.

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