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Menstrual Characteristics in Black Women with Systemic Erythematosus Lupus (SLE) in Atlanta, Georgia

By

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Master of Public Health

Epidemiology

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By

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Bachelor of Science
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Thesis Advisor: Penelope P. Howards, Ph.D.

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Abstract

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By Jasmine Berry

Objective Black women with SLE experience a more sever disease progression, more organ damage, earlier onset of disease, and higher disease activity than White women with SLE, which may make them more susceptible to developing secondary amenorrhea and experiencing fertility issues. This study evaluated the association between secondary amenorrhea and SLE among Black women.

Methods Women, ages 22-40, who lived in Metro Atlanta, were diagnosed with SLE at ages 18-35, did not have a hysterectomy, did not have a history of cancer, and were not receiving dialysis were eligible for the study. Women in Metro Atlanta were recruited via a marketing list for the comparison group. All women were interviewed about their medical and reproductive histories. Secondary amenorrhea was defined as an absent menstrual period for 3 months or more. Multivariate logistic regression was used to examine the association between SLE status and secondary amenorrhea and between type of SLE medication and secondary amenorrhea. Models were adjusted for age at interview, smoking status, and body mass index. Secondary analyses stratified on contraceptive use and on reproductive conditions.

Results The study population included 89 women with SLE and 163 women without SLE. Women with SLE had a higher odds of secondary amenorrhea compared to women without SLE (aOR: 3.0, 95% CI: 1.3-6.8). Mycophenolate mofetil was associated with secondary amenorrhea (cOR: 2.0, 95% CI: 0.7-5.6) but not azathioprine (cOR: 1.0, 95% CI: 0.4-2.7) among women with SLE. However, these associations were imprecise.

Conclusions Secondary amenorrhea is more prevalent among women with SLE compared to women without SLE. Some medications, but not others, may contribute to the occurrence of secondary amenorrhea.

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CHAPTER 1: LITERATURE REVIEW

Introduction

Systemic Lupus Erythematous (SLE) is a chronic, autoimmune disease that disproportionately affects women during their reproductive years. Organ damage is a common consequence of the disease progression and can result in dysfunction of the reproductive organs. This dysfunction can lead to the occurrence of primary ovarian failure (POF), which is characterized by impaired ovarian function and menstrual irregularities. Medications that are used to manage the symptoms and progression of SLE, such as cyclophosphamide and corticosteroids, have also been implicated in reproductive dysfunction. Previous evidence has suggested that the prevalence of menstrual irregularities among those with SLE is higher than women without SLE. However, important gaps in knowledge remain regarding menstrual function among Black women with SLE.

Compared to White women with SLE, Black women with SLE tend to experience a more severe disease progression, more organ damage, earlier onset of disease and higher disease activity. Therefore, they may be more susceptible to issues with their menstrual cycle compared to White women. Despite SLE being more prevalent among Black women, few studies have investigated menstrual characteristics in this population. Considering normal menstrual function is important for fertility; abnormal menstrual function can influence long-term family planning and the ability to meet reproductive goals. Therefore, it is important to analyze the extent to which menstrual functional is impaired in Black women with SLE.

Systemic Lupus Erythematosus (SLE) Background

SLE is a chronic, long-term autoimmune disease that is characterized by a dysfunction of the immune system, primarily due to the abnormal responses of B and T cells [1, 2]. B and T

cells form the adaptive immune system, which develops its response from past infections and vaccines to defend the body against subsequent infections [3]. B cells produce pathogen-specific antibodies that bind to, inactivate, and mark pathogens to be destroyed [4]. T cells modulate and contribute to B cells' mechanisms by encouraging the production of antibodies and destroying cells marked for destruction [3, 4]. This process can lead to tissue inflammation at the site of infection [1]. The defects in B and T cell activity result in pathogenesis of SLE, as these autoreactive antibodies attack the body's tissues and organs and create recurrent inflammation and damage in those areas [5, 6].

Symptoms and clinical manifestations of SLE can vary from mild to severe at disease onset and change in severity as the disease progresses [2, 7, 8]. The American College of Rheumatology developed criteria consisting of 11 assessments to diagnosed SLE [9, 10]. Patients must meet four of the 11 assessments to be diagnosed with SLE [7, 9]. Skin lesions are the most common symptom and can appear as a characteristic butterfly-shaped rash on the face and lesions on the arms, hands, chest, and neck [8]. Patients who have skin lesions may also experience photosensitivity. Additional symptoms include, but are not limited to, fatigue, joint and muscle pain, and fever [7, 10]. Due to constant tissue inflammation, patients with SLE are also prone to developing organ damage [11]. The majority of patients with SLE experience damage in the renal, musculoskeletal, cardiovascular, integumentary, pulmonary, reproductive, and peripheral vascular systems (8). Lupus Nephritis is a common and serious complication that affects kidney function [11]. Up to 50% of SLE patients will develop this complication within 5 to 10 years of diagnosis and may suffer from End-Stage Renal Disease (ESRD) [11, 12].

Epidemiology of SLE

Epidemiologic data on the incidence and prevalence of SLE vary as there is no national surveillance system of SLE [13]. Sites in Georgia, Michigan, California, and Tribal areas in Alaska, Phoenix, and Oklahoma City were funded by the CDC to measure SLE incidence and prevalence rates [13]. The surveillance period varied between sites, as sites in Georgia and Michigan were funded from 2002 to 2004 while sites in New York, California, and Tribal areas were funded from 2007 to 2009 [13]. Based on data collected from these sites, the pooled incidence is 5.1 cases per 100,000 person-years and the pooled prevalence is 72.8 cases per 100,000 person-years [14, 15]. SLE disproportionately affects women compared to men, with a prevalence rate that is approximately 9 times higher than that of men [15]. Disparities also exist by race and ethnicity among women as Black women with SLE have a prevalence that is approximately 3 times greater than their White counterparts [15].

Epidemiology of Menstruation and Amenorrhea

Menstruation is a biological function that involves the shedding of the uterine lining and typically has a 28 to 30 day-cycle [16]. The median age of reaching menarche, or first menses, is approximately 12.43 years of age, with 90% of females reaching menarche by age 14 [17, 18]. However, non-Hispanic black females reach menarche earlier than non-Hispanic white females [19]. It is estimated that 14% to 25% of women of childbearing age experience menstrual irregularities (20).

Amenorrhea is a menstrual disorder characterized by the absence or abnormal cessation of a menstrual cycle among females aged 12 to 49 years [21, 16]. Amenorrhea not due to

pregnancy, lactation, or menopause has a prevalence of 1% to 4% [21, 16]. This disorder can be classified as either primary or secondary amenorrhea.

Primary amenorrhea is commonly defined as the absence of a menstrual cycle by age 16 and has a prevalence of 1% to 2% among women [22, 23]. Genetic and developmental disorders are estimated to contribute to the development of 60% of cases. Endocrine and hormonal issues are estimated to contribute to 40% of cases [22, 24]. Secondary amenorrhea occurs due to the absence of a menstrual cycle for longer than 6 months and has an incidence of 3% to 5% among women [22, 23]. However, definitions used for this disorder vary based on the healthcare professional. This disorder may also be defined as the absence of 3 menstrual cycles [22]. In addition to the factors that contribute to primary amenorrhea development, ovarian dysfunction, and polycystic ovarian syndrome (PCOS) are also common causes of secondary amenorrhea in adults [22].

This disorder can lead to hormonal imbalances during the different stages of the menstrual cycle, which can affect the ability to ovulate [25, 26]. Fertility is dependent on ovulation, in which the ovaries release an egg that has a chance of being fertilized [27, 28]. Thus, amenorrhea can negatively impact fertility and future pregnancy chances.

Amenorrhea is often associated with primary ovarian failure (POF). Approximately 10-28% of women with POF will experience primary amenorrhea and 4-18% will experience secondary amenorrhea [29, 30]. POF typically occurs before the age of 40 years and is characterized by the irregular release of eggs by the ovaries [31]. It is estimated to have a prevalence of 1% among all women below the age of 40 and result in the loss of fertility in approximately 90% of women with this disorder [32, 33].

Reproductive Issues and SLE

Women with SLE may experience issues with their reproductive system. POF has been linked to reproductive issues in patients with SLE [34]. These issues may be affected by type of drug treatment and disease activity [35]. The estimates of the prevalence of POF among women with SLE vary, with the majority focusing on the prevalence among women receiving a drug treatment. A few studies have reported the prevalence of menstrual disorders and POF among women with SLE who had not received a drug treatment.

A cross-sectional study conducted by Mayorga et al. in Mexico assessed the prevalence of POF among women with SLE who were younger than 40 years [36]. Amenorrhea was estimated based on the time between the self-report date of the last menstrual period and the date of the interview. POF was defined as amenorrhea that lasted 12 months or longer and high follicle stimulating hormone (FSH) levels in women younger than 40 years old. Secondary amenorrhea was defined as an absent menstrual cycle for 12 months or longer and normal or low FSH levels. Sixty out of 961 patients (6.2%) experienced amenorrhea, of which 52 had POF (5.4%) and 8 had secondary amenorrhea (0.8%). The researchers found that the prevalence of POF among women who had never received cyclophosphamide was 0.6%, while the prevalence among women treated with cyclophosphamide was 16.7%. The researchers also noted that age at SLE diagnosis, drug treatment, disease activity, and renal damage were covariates that were associated with the occurrence of POF.

A study conducted in Brazil found similar results. Pasoto et al. examined menstrual function among 36 female patients with SLE, age 18-39 years old, who never received an alkylating drug treatment, which can negatively impact normal menstrual function [37]. A normal menstrual cycle was defined as ranging from 21 to 36 days, with 1-8 days of blood flow

and no blood clots. Menstrual disturbances were defined as a change in one or more of the parameters defined for a normal menstrual cycle for at least 3 consecutive cycles. These changes involved either an increase or decrease in blood flow or an increase or decrease in cycle length. Amenorrhea was defined as the absence of a menstrual cycle for 3 or more consecutive cycles. Seventeen of 36 patients (47%) had a normal menstrual cycle while 19 (53%) experienced a menstrual disturbance. Only 1 (2.8%) patient with SLE had amenorrhea. Disease activity was associated with menstrual irregularities with high disease activity being more prevalent among patients with menstrual disturbances compared to patients with normal cycles (37% vs 0%).

A population-based, cross-sectional study based on the Georgians Organized Against Lupus (GOAL) cohort estimated the prevalence of secondary amenorrhea among women with SLE treated with cyclophosphamide compared to those who were not treated with the drug [38]. Data was included from 147 women who were over the age of 40 at the time of the survey but were between the ages of 20-40 years at SLE diagnosis. Secondary amenorrhea was self-reported and defined as menstrual period that stopped before the age of 40. Use of cyclophosphamide prior to the age of 40 was also self-reported. Among women with SLE who had not been previously treated with cyclophosphamide (n=114), 17% (n=19) reported experiencing secondary amenorrhea. Among the women with SLE who had been previously treated with cyclophosphamide (n=33), 39% reported experiencing secondary amenorrhea. Women with SLE who had ever been treated with cyclophosphamide had an adjusted prevalence ratio that was 2.3 times (95% CI: 1.1-4.7) that of women who had never been treated with the drug. These results suggest that the prevalence of POF among women with SLE who do not receive drug treatment is similar to that in the general population. Contributing factors highlighted in these studies, such as age, disease activity, and drug activity, may play a significant contributing role in the

development of menstrual irregularities. However, the differences in age ranges and the definitions used for menstrual disorders and menstrual function across these studies makes it difficult to compare results as there may be unaddressed misclassification issues.

Black women with SLE are more likely than White women to experience an earlier onset of disease, more severe disease progression, more organ damage and clinical manifestations, and higher disease activity [39,40]. Several studies have investigated and confirmed these disparities among the LUMINA (Lupus in Minorities: Nature versus Nurture) cohort, which is composed of Hispanic, Black, and White women with SLE [41-43]. Considering disease activity has been reported to be significantly associated with menstrual irregularities, Black women may be at a higher risk of experiencing a menstrual disorder compared to White women. Although few of these studies have examined reproductive damage or amenorrhea, a longitudinal study by Gonzalez et al assessed premature gonadal failure among women in the LUMINA cohort [44]. Premature gonadal failure was defined as amenorrhea that lasted more than 6 months, was unrelated to hysterectomy, and/or all-cause menopause before age 40. Black women had a prevalence of premature gonadal failure that was twice as high as their White counterparts (12.0% vs 5.9%, respectively). Additionally, Black women had 2 times the hazard of premature gonadal failure compared to their White counterparts (HR = 2.0, 95% CI: 0.5 – 7.5). Thus, these results suggest that Black women with SLE may experience disproportionate reproductive dysfunction.

Effect of SLE Medications on Reproductive Health

Medications used to treat or manage SLE can also influence the degree of reproductive damage and menstrual irregularities [45]. Cyclophosphamide has been implicated in the development of POF due to its toxicity [45,46].

A study in Thailand investigated the prevalence of POF among 92 patients aged 18-40 who were receiving drug treatments for SLE [47]. A normal menstrual cycle was defined as lasting 21 to 35 days, with a menstrual period lasting fewer than 7 days. Amenorrhea was defined as the absence of a menstrual cycle for 6 consecutive months. An irregular menstrual cycle was defined as an absence of a menstrual cycle for 2 to 6 months, a menstrual cycle lasting either less than 21 days or more than 35 days, or a menstrual period lasting more than 7 days. Transient amenorrhea was defined as having a history of amenorrhea but having normal menstruation return spontaneously. POF was defined as having amenorrhea and an estradiol level that was ≤30pg/mL and an FSH level that was ≥40IU/L before the age of 40. Approximately 70% of patients received cyclophosphamide treatment. Among all study participants, 12% were diagnosed with POF, 38% had an irregular menstrual cycle, 11% had transient amenorrhea, and 13% had amenorrhea. Dose of cyclophosphamide was found to be a risk factor for developing POF. Patients with POF were more likely to have a cyclophosphamide dose that was higher than 10g (90% vs 35%) and have a longer cyclophosphamide treatment duration (47.4 +/- 24.8 months vs 7.5 +/- 10.2 months) than patients without POF. Additionally, among those with POF, cumulative doses of cyclophosphamide were higher than in patients without POF (34.9g +/- 33.1g vs 6.8g+/- 9.3g).

Another study in Greece assessed risk factors of sustained amenorrhea from intravenous cyclophosphamide among 67 women, age 20-46 years, with SLE [48]. Sustained amenorrhea was defined as a lack of a menstrual cycle for 12 months or more. Approximately, 31% (n=21) of patients developed amenorrhea. Disease duration was associated with sustained amenorrhea (HR=1.2, 95% CI: 1.0-1.4 when adjusted for age).

Similarly, a study in France examined the risk of ovarian failure in 56 women with SLE who who were younger than 55 years old and receiving cyclophosphamide [49]. Amenorrhea was defined as a lack of a menstrual cycle for 4 months. Sustained amenorrhea was defined as amenorrhea that lasted 12 months or more. Approximately 23% (n=13) patients developed sustained amenorrhea. Age at disease onset and cyclophosphamide initiation and disease duration were reported to be associated with ovarian failure. Women with ovarian failure were older at cyclophosphamide initiation than women who were menstruating (37 SD 7 years vs 26 SD 8 years). Age at SLE onset and years of SLE duration were also higher among women with ovarian failure compared to menstruating women. Menstruating women had an age at SLE onset of 22 years (SD 8 years), while women with ovarian failure had an age at onset of 28 years (SD 9 years). Time since SLE diagnosis for menstruating women was 9 years (SD 5 years) compared with 3 years (SD 3 years) for women with ovarian.

Medeiros et al. conducted a retrospective cohort study in Brazil that examined risk factors for ovarian failure among women, aged 16 to 45 years, with SLE [50]. Ovarian insufficiency was defined as amenorrhea that lasted longer than 4 months while amenorrhea that lasted 12 months or more was defined as premature menopause. They found that 15.5% (n=11) of 71 patients had ovarian failure while 11.3% (n=8) had premature menopause. Cyclophosphamide use was substantially higher among those with ovarian failure, compared to those with normal menstruation (81.8% vs 28.3%). Women using cyclophosphamide were 7.8 times more likely to develop ovarian failure compared to women who were not using the drug (95% CI: 1.8-33.3). Additionally, a cumulative dose greater than 10 g was associated with a 3.2 times higher risk of ovarian failure compared to a cumulative dose less than 10 g (95% CI: 1.0-10.0).

A cross-sectional study conducted by Tsaliki et al. investigated the impact of ovarian autoimmunity among women with SLE receiving cyclophosphamide [51]. Autoantibodies binding ovarian antigens were measured via an anti-ovarian antibody enzyme-linked immunosorbent assay. POF was considered to be premature menopause, in which there was a spontaneous cessation of menstrual periods prior to age 45. While the researchers did not find an association between ovarian autoimmunity and premature menopause, they did report that 65.5% (n=169) of the 258 women had premature menopause. However, they did not examine the association between cyclophosphamide use and menopause status.

Collectively, these results suggest that not only is POF more prevalent among those who use cyclophosphamide, but that higher dosages and older age can also influence the effect of the drug on the development of POF and amenorrhea among women with SLE. However, comparison of these results should be done with caution as many different definitions of POF and menstrual disorders were used and varying age ranges were included that could have impacted their results.

There is a gap in research on the impact of cyclophosphamide on reproductive function in Black women with SLE. Given that Black women with SLE have a more severe disease progression and worse clinical outcomes compared to White women, they may be more likely to receive cyclophosphamide or receive higher doses of the drug to manage their renal complications (52). Consequently, they could also be more susceptible to developing POF and experiencing menstrual irregularities.

Present Study

Currently, there is a gap in the literature that addresses menstrual irregularities among Black women with SLE. The present study aims to investigate the occurrence of secondary amenorrhea in Black women with SLE compared to Black women without SLE. Using Black women as the comparison group allows for analysis that considers and focuses on the singular experience of Black women. This perspective can have broader implications on fertility in Black women, inform patient-provider care for Black women, provide insight into the causes of racial disparities among those with SLE, and increase understanding about potential reproductive complications women with SLE may experience.

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CHAPTER 2: SECONDARY AMENORRHEA IN BLACK WOMEN DIAGNOSED WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN ATLANTA, GEORGIA

Systemic Lupus Erythematosus (SLE) is a chronic, long-term autoimmune disease that is characterized by the dysfunction of the immune system [1]. Tissue inflammation, organ damage, fatigue, and skin lesions are common symptoms and clinical manifestations among patients with SLE [2-4]. SLE has an estimated incidence of 5.1 cases per 100,000 person-years [5]. Women are disproportionately affected by this disease compared to men with a prevalence that is approximately 9 times higher than that of men [6]. SLE is approximately 3 times more prevalent among Black women compared with White women, and Black women are more likely to have more severe disease progression, organ damage, higher disease activity, and an earlier disease onset compared to White women [6-8].

Secondary amenorrhea is a menstrual disorder that is commonly defined either as the absence of 3 or more menstrual periods or the absence of menses for 6 months or more [9]. This disorder has an incidence of 3% to 5% in the general population and can be caused by endocrine disorders, hormonal imbalances, ovarian dysfunction, or polycystic ovarian syndrome (PCOS) [9-11]. Secondary amenorrhea can have negative implications on fertility and the ability to meet pregnancy goals through its impact on ovulation [12, 13]. From 4% to 18% of women experiencing amenorrhea will also experience POF (primary ovarian failure). POF is characterized by the irregular release of eggs by the ovaries before the age of 40 [14]. Although the prevalence of POF is only 1% in the general population, it can result in the loss of fertility among approximately 90% of women with the disorder [15, 16].

Previous studies have reported that women with SLE may experience secondary amenorrhea and POF at higher rates than that of the general population [17-23]. Cyclophosphamide, a medication that is commonly used to manage symptoms of SLE, has been

implicated in the development of secondary amenorrhea and is known to be an ovarian toxicant [24, 25]. High cyclophosphamide dosage, early age at SLE diagnosis, and high disease activity have been reported to be factors that are associated with developing secondary amenorrhea and POF [17-23]. However, prior studies were racially homogenous and used varying definitions of secondary amenorrhea and POF that conflict with traditional definitions, which limits their generalizability to other populations. Additionally, the association between secondary amenorrhea and other SLE medications is not well studied, which prevents further insight into the effects of other drug treatments on menstrual function.

Despite the disproportionate burden of SLE born by Black women, Black women with SLE have been underrepresented in the literature. One study that investigated reproductive disparities among women with SLE found that Black women had twice the hazard of premature gonadal failure compared to White women (HR = 2.02, 95% CI: 0.54 – 7.51) [26]. Considering Black women with SLE face a higher burden of disease compared to White women, they may be at a higher risk of suffering from secondary amenorrhea. Therefore, it is important to investigate the reproductive issues Black women with SLE may experience as it may have further implications for their fertility. To address this gap in literature, this study aims to examine the association between secondary amenorrhea and SLE among Black women.

Methods

Study Population

Data was obtained from LIFE (Lupus Impacting the Female Experience) pilot study, which focuses on the reproductive and fertility experiences of women with SLE. The LIFE study used data collected from participants that were recruited in the GOAL (Georgians Organized

Against Lupus) research cohort [27]. Participants from the GOAL cohort were enrolled from the Georgia Lupus Registry (GLR) and lupus clinics at Grady Memorial Hospital and Emory University [28]. These participants resided primarily in Fulton and Dekalb counties, which have a large population of Black patients with SLE.

SLE was defined using the American College of Rheumatology Classification criteria for SLE. Those who met 4 ACR criteria or met 3 ACR criteria with an official diagnosis of SLE from a rheumatologist were defined as having SLE. One hundred women were recruited by phone, e-mail notices, and in-person at lupus clinics at Emory University and Grady Memorial Hospital. Women were considered eligible if they were 22-40 years of age at the time of enrollment, diagnosed with SLE at ages 18-35, did not have a hysterectomy, did not have a history of cancer, and were not receiving dialysis. Eligible women were then interviewed in-person about their reproductive and fertility histories. Height and weight were measured at the time of the interview while race was self-identified. Written informed consent was obtained before the start of the interview. Participants were also compensated for their time and travel. This cohort was further restricted to women who identified as Black/African American, resulting in a sample size of 89 women.

Women without cancer enrolled in the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study were used as the comparison group. Participants were recruited via a marketing list and completed a computer assisted telephone interview that consisted of the same questions used in the LIFE study. To allow for comparison across studies, the comparison group was restricted to Black/African American women, 22-40 years of age, who did not have a hysterectomy, and who lived in Metropolitan Atlanta. This

resulted in a comparison group of 163 women. Oral informed consent was obtained before the start of the interview, and participants were compensated for their time

The outcome, secondary amenorrhea, was defined as experiencing an absence of menses for 3 months or more based on the question: “Since you turned 20, have you ever gone 3 months or 90 days or more without a menstrual period?”. This definition excluded times when the participant was pregnant, breastfeeding, had a hysterectomy, had experienced menopause, or was using hormonal contraceptives. Occurrence of a lupus flare during a menstrual absence was self-reported using the following question: “When your periods stopped after your lupus diagnosis, were you having a lupus flare?”. Women reporting secondary amenorrhea were asked whether they were using any of the following medications at that time: cyclophosphamide, steroids, methotrexate, or another lupus medication.

Age at interview was self-reported. Self-reported smoking status was categorized as “current smoker”, “former smoker”, or “never smoker”. Current smoker and former smoker were later combined to create an “ever smoker” category during analysis because of small sample size. BMI was calculated using the patients’ weight and height that was measured at the time of interview for women in the LIFE Study and was self-reported for women in the FUCHSIA Women’s Study and using the formula: weight in kilograms divided by height in meters squared. Hormonal contraceptive use was measured using the question: “Have you ever taken hormonal contraceptives such as the pill, the patch, a Mirena, or Norplant?”. Diagnoses of reproductive conditions, such as fibroids, endometriosis, and Polycystic Ovarian Syndrome (PCOS) were based on self-reported diagnosis of the condition. Women also reported whether they had an endometrial ablation. Due to small sample size, all reproductive conditions and having an

endometrial ablation were combined into one category. Participants were asked about whether they had ever used a list of commonly used lupus treatments.

Statistical Analysis

We used multivariate logistic regression analysis to examine the association between SLE and secondary amenorrhea. We identified confounders using directed acyclic graphs informed by the literature. Model 1 was an unadjusted model that assessed the association of SLE status on secondary amenorrhea. Model 2 adjusted for BMI, smoking, and age at interview. We stratified by contraception use for Models 3 (ever use) and 4 (never use). For models 5 and 6, we stratified on diagnosis with a reproductive condition (ever and never). Both sets of stratified models were adjusted for BMI, smoking, and age at interview. In a secondary analysis, we examined the association between type of SLE medication/treatment and secondary amenorrhea among women with SLE. Mycophenolate mofetil and azathioprine were included in separate models. The treatment analyses were unadjusted because of the sample size. We could not evaluate other medications because either the majority of women with SLE took the medication (i.e., steroids and hydroxycholoquine sulfate) or very few women took the medication (i.e., methotrexate, cyclophosphamide, and benlysta).

Results

Table 1 presents the demographic characteristics of the study participants. Eighty-nine women with SLE and 163 women without SLE were included in the analysis. On average, women with SLE were younger (32.7 years, SD 5.3) than women without SLE (35.3 years, SD 4.0). A greater proportion of women with SLE were obese (42.7% and 36.3%). Women with and without SLE reported a similar average age at menarche (12.2 years, SD 1.7 vs. 12.3 years, SD

1.7). Compared to women without SLE, women with SLE were slightly less likely to have ever had a regular cycle after age 20 (83.1% vs 84.7%) and more likely to have stopped menses for 3 months or more (21.3% vs 9.6%) and for 12 months or more (6.7% vs. 1.2%). Women with and without SLE were just as likely to ever use hormonal contraceptives (75.3% vs 75.5%). However, women with SLE were less likely to use hormonal contraceptives in the past 12 months compared to women without SLE (19.1% vs 28.2%). Women SLE were less likely to be diagnosed with a reproductive condition (including a condition requiring an endometrial ablation) compared to women without SLE (25.8% vs 39.5%). Fibroids were the most diagnosed reproductive conditions for both groups of women, with women with SLE being less likely to be diagnosed with fibroids compared to women without SLE (13.5% vs 27.2%). Although women with SLE were more likely to have ever been pregnant compared to women without SLE (83.1% vs 74.1%), both groups of women were just as likely to have 1 or more children (67.4% vs 66.3%). Approximately half of women with SLE were single (49.4%) compared to 38% of women without SLE. Twenty-one percent of women with SLE had ever smoked compared to 6.2% of women without SLE.

Women with SLE had an average age at diagnosis of 24.3 years (SD 5.14). Among women with SLE, almost all women had ever used steroids (89.9%) and hydroxycholoquine sulfate (93.3%). Less than half of women with SLE had ever used mycophenolate mofetil (39.3%) and azathioprine (42.7%). Fewer women with SLE had ever used methotrexate (15.7%), cyclophosphamide (14.6%), benlysta (10.1%), or other medications (20.2%).

Fourteen percent of study participants reported secondary amenorrhea (Table 2). On average, women reporting secondary amenorrhea (35.0 years, SD 4.7 years) were of a similar age as women not reporting secondary amenorrhea (34.2 years, SD 4.7 years). Both women

reporting and not reporting secondary amenorrhea were most likely to be obese, and the average age at menarche was 12 years of age (SD 1.7) for both groups. However, women with secondary amenorrhea were more likely to report never having a regular cycle after age 20 compared to women not reporting secondary amenorrhea (52.9% vs 8.0%). Although women with secondary amenorrhea were more likely to report ever use hormonal contraceptives (82.4% vs 74.1%), they were slightly less likely to report using hormonal contraceptives in the past 12 months (20.6% vs 25.5%). The proportion of women reporting being diagnosed with a reproductive condition or having an endometrial ablation was similar in both groups with fibroids being the most commonly reported condition. The proportion of women who had ever been pregnant was similar for women with and without secondary amenorrhea (76.5% vs 77.3%). Women with secondary amenorrhea were slightly less likely to have 1 or more children (61.8% vs 67%). Over half of women with secondary amenorrhea were single (55.9%), compared to 41% of women who did not report secondary amenorrhea. Eighty-five percent of women with secondary amenorrhea never smoked compared to 89% of women not reporting secondary amenorrhea.

Among the women with SLE, women with secondary amenorrhea were diagnosed with SLE at a similar age (25.2 years, SD 4.5) as women not reporting secondary amenorrhea (24.1 years, SD 5.3). The most common medications ever used by both groups of women with SLE were steroids (84.2% and 91.4%) and hydroxycholoquine sulfate (94.7%and 92.9%). Approximately 52.6% of women with secondary amenorrhea and SLE had a history of using mycophenolate mofetil while 35.7% of women with SLE not reporting secondary amenorrhea used the drug. Similar proportions of both groups of women had a history of using azathioprine (42.1% and 42.9%). Few women of both groups had a history of using methotrexate (5.3% and 18.6%), cyclophosphamide (15.8% and 14.3%), benlysta (10.5% and 10.0%), and other

medications (21.1% and 20%). Among women with SLE reporting secondary amenorrhea, 21.1% of them reported having a flare when their periods stopped and 52.6% reported they were taking a SLE medication when their periods stopped. Among women with SLE reporting secondary amenorrhea, 53% reported that they were taking steroids when their periods stopped, 5.3% were using methotrexate, 10.5% were using cyclophosphamide, and 94.7% were using other medications.

In the unadjusted analysis, women with SLE were more likely to report ever having secondary amenorrhea compared to women without SLE (OR: 2.6, 95% CI: 1.2-5.4) (Table 3). This association was strengthened after adjusting for BMI, smoking status, and age at interview (OR: 3.0, 95% CI: 1.3-6.8). Among women who had ever used contraceptives, the odds of secondary amenorrhea among women with SLE was almost 3 times that among women without SLE (OR: 3.0, 95% CI: 1.2-7.4). Among those who had never used contraceptives, this association was similar (OR: 2.8, 95% CI: 0.4-22.1) although the estimate was imprecise. The odds of secondary amenorrhea for women with SLE was approximately 3 times that of women without SLE both for women who reported being diagnosed with any reproductive condition (OR: 3.2, 95% CI: 0.7-14.8) and for those not reporting any reproductive conditions (OR: 3.3, 95% CI: 1.1-9.8).

The odds of ever having secondary amenorrhea among women with SLE who had a history of taking mycophenolate mofetil was twice the odds of women with SLE who did not have a history of taking mycophenolate mofetil (OR: 2.0; 95% CI: 0.72-5.57) (Table 4). However, the association between azathioprine and ever having secondary amenorrhea was approximately null among women with SLE (OR: 1.0; CI: 0.4-2.7).

Discussion

The present study examined the association between SLE status and secondary amenorrhea, defined as absence of menses for 3 months or longer. Secondary amenorrhea was more prevalent among women with SLE compared to women without SLE, and this persisted after adjusting for potential confounders. Further, the magnitude of the association was similar when stratifying by contraceptive use (ever and never) and reproductive conditions, including conditions requiring an endometrial ablation, (any and none) although the estimates for some strata were imprecise. Women with SLE who had a history of taking mycophenolate mofetil had a higher odds of experiencing secondary amenorrhea while the effect of azathioprine was null, however these associations were imprecise.

These results were comparable to results from previous studies that investigated amenorrhea and menstrual irregularities among women with SLE. However, definitions for secondary amenorrhea varied considerably from study to study. Among SLE studies that defined amenorrhea as no menses for 12 months or more, the prevalence of this condition ranged from 0.8% to 31% [18, 29-31]. We found that 6.7% of women with SLE had no menses for 12 months or more, which fits within this range, but the number of women meeting this definition was too small for further analyses. There were a few studies of women with SLE that assessed menstrual absences for less than 12 months. However, no study had the same definition of secondary amenorrhea. In a study by Medeiros et al., 15.5% of women with SLE reported amenorrhea defined as no menses for 4 months or more [22]. In contrast, Pasoto et al. reported that only 2.8% of women with SLE reported 3 or more consecutive months without menses [18]. Additionally, in a study by Akwatcharangura et al., 38% of women with SLE had no menses for 2 to 6 months [31]. In our study, 21.3% of women with SLE reported experiencing no menses for 3 months or

more, which is higher than the prevalence found by both Medeiros et al. and Pasoto et al. but lower than that found by Akwatcharangura et al. These differences could be due to the time frame in which secondary amenorrhea was measured, as this study examined ever experiencing secondary amenorrhea during the patients' life after age 20 while other studies only reported instances of secondary amenorrhea that occurred during the study period.

This study was impacted by several limitations. The small sample size resulted in imprecise estimates for some models. Further, it prevented us from controlling for confounding when examining the association between medication and secondary amenorrhea. The sample size also prevented us from examining several of the most commonly used medications, which have been suggested to influence the development of secondary amenorrhea. Much of the data was self-reported by the participants, which could cause measurement error. We did not have information on medication dosage, which has been suggested to impact menstrual function, and therefore could not control for it. Additionally, we did not have information on the participants' disease severity, which could be a potential confounder. Since we only asked about 3 months and 12 months of amenorrhea, we were unable to assess if this experience was clinically meaningful. Yet, this study is one of the first studies to investigate secondary amenorrhea among Black women with SLE and to use Black women without SLE as a comparison group. Considering that Black women experience a more severe disease progression, more organ damage, earlier onset of disease and higher disease activity than white women with SLE, it is important to study how SLE affects the reproductive health of Black women.

Although the literature and the current study agree that women with SLE are more likely to experience secondary amenorrhea, the clinical significance is unclear. Prospective studies with larger sample sizes are also needed to investigate the extent to which common SLE medications

have short- and long-term effects on secondary amenorrhea. Since menstrual function is important for fertility, secondary amenorrhea may be an indication for infertility. In fact, in our cohort, Black women with SLE were more likely to experience a period of infertility compared to Black women without SLE [32]. Further, we found that women with SLE who had a history of cyclophosphamide treatment were more likely to have low anti-Müllerian hormone, a marker of ovarian reserve, compared to Black women with SLE who did not have a history of cyclophosphamide treatment [33]. Therefore, the occurrence of secondary amenorrhea could provide insight into future fertility issues and be used to inform family planning sessions for women with SLE.

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Tables

Table 1. Demographic and reproductive characteristics of study participants with SLE (N=89) and without SLE (N=163)

	SLE + (N=89)		**SLE – (N=163)**	
	N	%	N	%
Age at interview				
22-30	11	12.4	5	3.1
31-34	25	28.1	13	8.0
35-37	18	20.2	52	31.9
38-40	35	39.3	93	57.1
Body Mass Index (BMI)				
Underweight (<18.5 kg/m2)	3	3.4	2	1.3
Normal weight (18.5 – <25 kg/m2)	24	27.0	44	27.5
Overweight (25 – <30 kg/m2)	24	27.0	56	35.0
Obese (≥30 kg/m2)	38	42.7	58	36.3
Missing	0		3	
Age at menarche				
≤11	30	33.7	46	28.4
12	22	24.7	57	35.2
13	21	23.6	32	19.8
≥14	16	18.0	27	16.7
Missing	0		1	
Ever had regular cycle after age 20				
Yes	74	83.1	138	84.7
No	15	16.9	20	12.3
N/A (Always on hormonal contraceptives)	0	0.0	5	3.1
Absence of a menstrual cycle - 3 months or more				
Yes	19	21.3	15	9.6
No	70	78.7	142	90.4
Missing	0		6	
Absence of a menstrual cycle – 12 months				
Yes	6	6.7	2	1.2
No	83	93.3	161	98.8
Ever Hormonal Contraceptive Use				
Yes	67	75.3	123	75.5
No	22	24.7	40	24.5
Hormonal Contraceptive Use in Past 12 Months				
Yes	17	19.1	46	28.2
No	72	80.9	117	71.8

Reproductive Conditions[a]				
Fibroids	12	13.5	44	27.2
Endometriosis	4	4.5	8	4.9
Polycystic Ovarian Syndrome (PCOS)	4	4.5	7	4.3
Endometrial Ablation	3	3.4	5	3.1
None	72	80.9	106	65.4
Missing	0		1	
Ever been pregnant				
Yes	74	83.1	120	74.1
No	15	16.9	42	25.9
Missing	0		1	
Number of children				
0	29	32.6	55	33.7
1	20	22.5	38	23.3
2	22	24.7	39	23.9
3 or more	18	20.2	31	19.0
Relationship status				
Married	8	9.0	74	45.4
Living with partner	22	24.7	13	8.0
In committed relationship	14	15.7	14	8.6
Single	44	49.4	62	38.0
Other	1	1.1	0	0.0
Smoking Status				
Current smoker	10	11.2	4	2.5
Former smoker	9	10.1	6	3.7
Never smoker	70	78.7	153	93.9
Age at SLE diagnosis (years)[c]				
18-20	24	27.0		
21-25	35	39.3		
26-30	16	18.0		
31-35	14	15.7		
Medication ever use[b]				
Steroids	80	89.9		
Hydroxycholoquine Sulfate (Plaqenil)	83	93.3		
Methotrexate (Rheumatrex, Trexail)	14	15.7		
Cyclophosphamide (Cytoxan)	13	14.6		
Mycophenolate Mofetil (Cellcept)	35	39.3		
Azathioprine (Imuran)	38	42.7		
Benlysta (Belimumab)	9	10.1		
Other medications	18	20.2		
None	0	0.0		

SLE: Systematic Lupus Erythematosus

[a]Women could have reported more than one reproductive condition

[b]Women could have used more than one medication

Table 2. Menstrual characteristics of study participants with a menstrual absence for 3 months or more (N = 34) and with normal menstruation (N = 212)

	Menstrual absence for 3 months or more (N=34)		**Normal Menstruation (N=212)**	
	N	%	N	%
Age at interview				
22-30	2	5.9	14	6.6
31-34	5	14.7	33	15.6
35-37	7	20.6	62	29.2
38-40	20	58.8	103	48.6
Body Mass Index (BMI)				
Underweight (<18.5 kg/m2)	0	0.0	5	2.4
Normal weight (18.5 – <25 kg/m2)	8	24.2	58	27.6
Overweight (25 – <30 kg/m2)	9	27.3	69	32.9
Obese (≥30 kg/m2)	16	48.5	78	37.1
Missing	1		2	
Age at menarche				
≤11	11	32.4	61	28.9
12	13	38.2	64	30.3
13	6	17.6	47	22.3
≥14	4	11.8	39	18.5
Missing	0		1	
Ever had regular cycle after age 20				
Yes	16	47.1	195	92.0
No	18	52.9	17	8.0
Ever Hormonal Contraceptive Use				
Yes	28	82.4	157	74.1
No	6	17.6	55	25.9
Hormonal Contraceptive Use in Past 12 Months				
Yes	7	20.6	54	25.5
No	27	79.4	158	74.5
Reproductive Conditions[a]				
Fibroids	9	26.5	47	22.2
Endometriosis	3	8.8	9	4.2
Polycystic Ovarian Syndrome (PCOS)	6	17.7	4	1.9
Endometrial Ablation	1	2.9	7	3.3
None	20	58.8	153	72.6

Missing	0		1	
Ever been pregnant				
Yes	26	76.5	163	77.3
No	8	23.5	48	22.7
Missing	0		1	
Number of children				
0	13	38.2	70	33.0
1	5	14.7	52	24.5
2	8	23.5	52	24.5
3 or more	8	23.5	38	17.9
Relationship status				
Married	6	17.6	72	34.1
Living with partner	8	23.5	26	12.3
In committed relationship	1	2.9	27	12.8
Single	19	55.9	86	40.8
Other	0	0.0	1	0.5
Smoking Status				
Current smoker	4	11.8	10	4.7
Former smoker	1	2.9	13	6.1
Never smoker	29	85.3	189	89.2
Age at SLE diagnosis (years)[c]				
18-20	2	10.5	22	31.4
21-25	9	47.4	26	37.1
26-30	6	31.6	10	14.3
31-35	2	10.5	12	17.1
Medication ever use[b, c]				
Steroids	16	84.2	64	91.4
Hydroxycholoquine Sulfate (Plaqenil)	18	94.7	65	92.9
Methotrexate (Rheumatrex, Trexail)	1	5.3	13	18.6
Cyclophosphamide (Cytoxan)	3	15.8	10	14.3
Mycophenolate Mofetil (Cellcept)	10	52.6	25	35.7
Azathioprine (Imuran)	8	42.1	30	42.9
Benlysta (Belimumab)	2	10.5	7	10.0
Other medications	4	21.1	14	20.0
None	0	0.0	0	0.0
Having a flare when periods stopped after SLE diagnosis[c]				
Yes	4	21.1		
No	15	78.9		

Medication used when periods stopped[b, c]		
Steroids	10	52.6
Methotrexate (Rheumatrex, Trexail)	1	5.3
Cyclophosphamide (Cytoxan)	2	10.5
Other medications	10	52.6
None	9	47.4

SLE: Systematic Lupus Erythematosus

[a]Women could have reported more than one reproductive condition

[b]Women could have used more than one medication

[c]All SLE variables are limited to women with SLE (19 with amenorrhea, 70 without amenorrhea)

Table 3. Crude and adjusted odds ratios of amenorrhea among women with SLE (N=34) compared to women without SLE (N=212)

	Amenorrhea	N	OR	95% CI
All, unadjusted				
SLE	19	89	2.6	1.2 – 5.4
Comparison	15	163	1.0	
All, adjusted[b]				
SLE	19	89	3.0	1.3 – 6.8
Comparison	14	154	1.0	
Ever used hormonal contraception, adjusted[b]				
SLE	16	67	3.0	1.2 – 7.4
Comparison	12	117	1.0	
Never used hormonal contraception, adjusted[b]				
SLE	3	22	2.8	0.4 – 22.1
Comparison	2	37	1.0	
Ever diagnosed with a reproductive condition, adjusted[a, b]				
SLE	7	17	3.2	0.7 – 14.8
Comparison	7	55	1.0	
Never diagnosed with a reproductive condition, adjusted[a, b]				
SLE	12	72	3.3	1.1 – 9.8
Comparison	7	98	1.0	

CI: Confidence Interval, OR: Odds Ratio, SLE: Systematic Lupus Erythematosus

[a] All reproductive conditions (fibroids, endometriosis, polycystic ovarian syndrome (PCOS)) and endometrial ablation were grouped together into one category during analysis

[b] Adjusted models control for age at interview (22-30, 31-34, 35-37, 38-40), BMI (underweight, normal weight, overweight, and obese), and smoking status (ever smoker, never smoker)

Table 4. Crude odds ratios of the effect of medications on secondary amenorrhea among women with SLE (N=34)

	Amenorrhea	N	OR	95% CI
Mycophenolate Mofetil				
Yes	10	35	2.0	0.7 - 5.6
No	9	54	1.0	
Azathioprine				
Yes	8	38	1.0	0.4 - 2.7
No	11	51	1.0	

CI: Confidence Interval, OR: Odds Ratio, SLE: Systematic Lupus Erythematosus