Published in final edited form as:

Lupus. 2021 February ; 30(2): 204–210. doi:10.1177/0961203320973074.

A prospective study of reproductive factors in relation to risk of systemic lupus erythematosus among black women

Yvette C Cozier, DSc, MPH¹, Medha Barbhuiya, MD, MPH², Nelsy Castro-Webb, ALM¹, Karen H Costenbader, MD, MPH³, Lynn Rosenberg, ScD¹

¹Slone Epidemiology Center at Boston University, Boston, MA;

²Rheumatology, Department of Medicine, Hospital for Special Surgery, New York, NY,

³Division of Rheumatology, Inflammation and Immunity, Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Objective.—Systemic lupus erythematosus (SLE) occurs most commonly among reproductive age women, compatible with a potential role of reproductive factors, although past studies including women of mainly European ancestry have yielded conflicting results. We assessed relationships of reproductive factors to SLE risk among black women.

Methods.—We followed 58,243 participants in the Black Women's Health Study (BWHS) from 1995 – 2015 using biennial health questionnaires, on which participants reported reproductive and other factors. Self-reported incident SLE cases were confirmed as meeting 1997 American College of Rheumatology SLE classification criteria by medical record review. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for SLE for several reproductive factors, controlling for potential confounders.

Results.—During 954,476 person-years of follow-up, 125 incident cases of SLE were confirmed. Later age at menarche and longer duration of breast feeding were associated with increased risk of SLE. The multivariable HRs were 2.31 (95% CI, 1.30–4.11) for age at menarche 15 relative to age 12, and 1.73 (95% CI, 1.01 – 2.94) for breast feeding 6 months relative to none. There were no clear associations with parity, age at first birth, menopausal status, hysterectomy, age at menopause, or history of endometriosis.

Conclusion.—Our results suggest that later menarchal age and breastfeeding of infants for 6 months vs. none may be associated with increased SLE risk among black women, while other reproductive factors did not appear related. The biological mechanisms underlying these potential associations should be pursued.

Corresponding author and reprint requests: Yvette Cozier, DSc, Slone Epidemiology Center at Boston University, 72 East Concord St, Boston, MA 02118; Phone: 617-206-6165; FAX: 617-738-5119; yvettcc@bu.edu.

Declaration of Conflicting Interest

The Authors declare that there is no conflict of interest.

Keywords

reproduction; parity; menopause; menarche; lactation; systemic lupus erythematosus; SLE; prospective; risk factor; black women

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects women more than men, and black women more than women of other racial/ethnic groups.^{1–3} As SLE has its peak incidence in women during the reproductive years at ages 15 to 40, increasing after menarche and declining after menopause, research has focused on potential reproductive and menopausal risk factors. However, results of past studies have been somewhat conflicting and inconclusive.^{4–6} In the present study, we assessed reproductive factors, including age at menarche, parity, age at first birth, breastfeeding, menopausal status, hysterectomy, and endometriosis in relation to SLE risk in a prospective cohort study of black women, a population at high risk of SLE. We hypothesized that early age at menarche and menopausal status would be associated with increased risk of SLE as they have been in cohorts of white women.⁶

Methods

The Black Women's Health Study (BWHS).

In 1995, black women ages 21–69 years (median 38 years) from the continental U.S. enrolled in the BWHS by completing 14-page health questionnaires; the 59,000 women with valid addresses a year later have been followed by biennial questionnaires, on which they provide demographic, medical and lifestyle information.^{7,8} Yearly linkage with the National Death Index was used to identify deaths. Follow-up has been successful for >85% of potential person-years through 2015. The Institutional Review Board of Boston University Medical Center approved the study. Participants indicate their consent by filling out the questionnaires; they sign consents for obtainment of medical records.

Reproductive factors.

Participants provided data on age at menarche (<11, 11, 12–14, 15 years) at baseline in 1995. Self-reported parity, age at first birth (years), number of children, menopausal status (including hysterectomy), age at menopause (years), and endometriosis were obtained in 1995, and updated on subsequent biennial questionnaires. Questions on lactation (never, ever) (including duration (months)) were asked in 1995, 1999, 2003, 2005, and 2011 questionnaires.

Covariates.

Data on current height (inches), and weight (pounds) at age 18 were collected at baseline in 1995. Additional covariate variables, including current weight was used to calculate body mass index (BMI) (>25, 25–29, 30 kg/m²), cigarette smoking (never, past, current), and alcohol consumption (never, past, current), and use of female hormone replacement therapy (ever, never) were obtained in 1995, with updates on subsequent biennial questionnaires.

Age began alcohol consumption (≤ 14 years, >14 years/never), age began smoking (≤ 14 years, >14 years/never), age began oral contraceptive use (≤ 14 years, >14 years/never), and BMI at age 18 (<20 , 20–24, 25–29, ≥ 30 kg/m²), were also obtained in 1995. Experiences of childhood sexual abuse (ever, never) and physical abuse (ever, never) were collected in 2005, and completed parental education (neither parent attended college, at least one parent attended college, at least one parent college graduate) was collected in 2009.

SLE cases.

The 1995 questionnaire asked about a list of diagnoses that included “lupus”. Every subsequent biennial questionnaire asked about “lupus (systemic lupus erythematosus)” and the date of diagnosis. The doctors of women who gave consent were asked to provide copies of medical records concerning SLE or to fill out a checklist about the presence of the 1997 Updated American College of Rheumatology (ACR) criteria for Classification of SLE.^{9,10} Medical record review by study rheumatologists (KC, MB) confirmed cases as the presence of at least 4 of the ACR SLE classification criteria.

Analytic cohort.

The current analysis assessed data from the baseline questionnaire through ten subsequent follow-up cycles (1995–2015). We excluded 757 women who reported SLE diagnosed before study entry in 1995. The remaining 58,243 women comprised the analytic cohort.

Statistical analysis.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of reproductive variables with risk of SLE. Women contributed person-time over ten biennial questionnaire cycles from baseline in 1995 until SLE diagnosis, death (N=6,315), loss to follow-up (N=4,328), or end of follow-up (2015), whichever occurred first (Figure 1). Women who reported SLE, but for whom we were unable to obtain medical records to confirm the diagnosis, were censored at the year of self-reported diagnosis.

Cox models were jointly stratified by age in 1-year intervals and questionnaire cycle (model 1). We examined age at menarche, parity, age at first birth, lactation, menopause, and endometriosis as individual predictors of SLE. The multivariable model examining age at menarche as the predictor included the following covariates from close to the time of menarche: age began alcohol consumption, age began smoking, age began oral contraceptive use, BMI at age 18, and completed parental education. A second model additionally adjusted for ever experiencing childhood sexual abuse and childhood physical abuse. The multivariable models for the remaining variables (menopause, parity, age at first birth, lactation, and endometriosis) adjusted for the following: alcohol status, smoking status, BMI, BMI at age 18, parity, menopausal status (except for menopause), current use of oral contraceptives, ever use of female hormone, and age at menarche. Tests for trend were performed by entering continuous variables in the multivariable models, using the median value within each category as appropriate.

Results

During 954,476 person-years of follow-up from entry in 1995 to 2015, 125 incident cases of SLE were confirmed: the mean age at diagnosis was 43 years, the mean number of 1997 ACR criteria for SLE was 5.0 (± 1.2), 64% had hematological and 30% had renal involvement (Table 1). Table 2 displays the baseline demographic and reproductive characteristics of the BWHS cohort and SLE cases in 1995. Compared to the BWHS cohort, SLE cases were slightly older at baseline, more educated, less likely to smoke, were younger at first birth, and more likely to report ever use of female hormones.

As shown in Table 3, the HR for SLE increased, but not significantly with increasing age at menarche (p trend= 0.08). We utilized multivariable models with and without adjustment for childhood sexual and physical abuse. The multivariable HR for SLE for onset of menarche at 15 years or older relative to menarche at age 12, the mean in the cohort, was 2.29 (95% CI, 1.29–4.06); after additional adjustment for childhood sexual and physical abuse the HR was 2.31 (95% CI, 1.30–4.11). Early menarche (<11 years) was not statistically associated with increased risk of SLE: HR=1.31 (95% CI, 0.72, 2.39).

Parity, age at first birth, and number of children were not related to SLE risk. The multivariable-adjusted HR associated with breast feeding for at least 6 months relative to none was 1.73 (95% CI, 1.01 – 2.94). When we further assessed longer duration of lactation the multivariable HR for 12 months (13 cases) was unchanged at 1.73 (95% CI, 0.90–3.34). There were no consistent increases or decreases in SLE risk across having had a hysterectomy, age at menopause, or endometriosis.

Discussion

In the present study, late onset of menarche was associated with an increased risk of SLE: the HR for onset of menarche at age 15 or older compared to the cohort mean of 12 years, was more than doubled. A study by Parks et al,¹¹ reported that among postmenopausal women in the National Health and Nutrition Examination Survey (NHANES; 1999–2004), ANA prevalence was associated with an older age at menarche ($p=0.019$; age 16–20 versus 10–12 years POR=3.0, 95%CI 1.6, 5.9). Late age at menarche was also previously associated with increased SLE risk in a case-control study of Japanese women (282 cases).⁵ However, SLE risk was elevated for early age at menarche, at 10 or younger, rather than late age in the Nurses' Health Study and the Nurses' Health Study II cohorts, composed primarily of White women. No association was found for age at menarche and SLE in a case-control study from North and South Carolina with 240 cases, of whom almost two-thirds were black.⁴ In the current study, the HR for SLE among those who reported the youngest age at menarche (< age 11) was also elevated at 1.31, but with only 17 cases in this category this result was not significant.

Age at menarche may be a marker for stress-mediated effects on the immune system, such as child abuse, which may in turn influence risk of SLE. For example, Boynton-Jarrett and colleagues found that severity of childhood sexual abuse was associated with risk for early menarche, while physical abuse was associated with both early and late menarche in the

NHS II cohort.¹² In analyses involving the BWHS, Wise et al. found that both childhood sexual and physical abuse were positively associated with early menarche.¹³ Recent analyses in both the NHS II¹⁴ and the BWHS¹⁵ have each found associations between childhood physical and sexual abuse and risk of SLE. For that reason, we controlled for both childhood sexual and physical abuse in the current analysis, but this did not materially change the estimates.

Ellis's theory of stress reactivity¹⁶ hypothesizes a U-shaped (curvilinear) association between early life adversity and stress reactivity. For example, family support or stress may influence the hypothalamic-pituitary-gonadal (HPG) axis in response to early adversity, resulting in either pathway hyper-activation (early menarche) or suppression (late menarche). We did not assess types or levels of family support in our analyses.

With regard to parity, risk of SLE was decreased in the Japanese study,⁵ and unassociated in the NHS,⁶ the Carolina study,⁴ and the present study.

Several studies have associated high levels of prolactin in blood with SLE disease activity or development in humans¹⁷ and mouse models.¹⁸ Prolactin is a hormone primarily secreted by the pituitary gland and has stimulatory effects on the immune system. Prolactin stimulates the production of milk in breastfeeding mothers, and serum levels of prolactin increase minutes after breastfeeding.¹⁹ Breastfeeding for over 6 months, compared to never breastfeeding, was associated with an increased risk of SLE in the multivariable-adjusted models in the present study, although the risk was not further elevated among those who breastfed their babies for 12 months or more, and it is not clear that this is more than a chance finding. In contrast, duration of lactation was inversely associated with risk in the Carolina Study,⁴ and not associated in the NHS.⁶ The relationship between long-term breastfeeding, prolactin levels, and SLE needs further investigation.

Earlier age at menopause (<47 years) was associated with a greater than two-fold increased risk of SLE among women in the NHS cohort.⁶ This increase, however, was observed primarily among those women who had undergone bilateral oophorectomy (surgical menopause) and were therefore younger at the onset of menopause.

There was no clear association with age at menopause or with hysterectomy in the present study.

History of endometriosis was associated with increased SLE risk in the NHS,²⁰ and with a non-significant increased risk among whites but not blacks in the Carolina study,⁴ whereas there was no significant association in the present study based on only 14 SLE cases reporting endometriosis.

The present study has several strengths. The data were collected using a prospective cohort study design, minimizing the possibility of reporting bias. Potential SLE cases were reviewed and confirmed by study rheumatologists to meet the ACR classification criteria for SLE. A number of potential confounding factors were controlled in the analysis. Study limitations include limited statistical power because of the relatively small number of incident SLE cases. We conducted multiple tests which increased the possibility of false

positives. Additionally, several of the reproductive factors and the child abuse exposure information were collected retrospectively. The BWHS is not a probability sample. Participants must be literate to complete mailed questionnaires and they underrepresent the 15% of US black women nationally who have not completed high school.²¹ Conversely, participants reside in all regions of the United States. Thus, the present results might apply to a large population of U.S. black women.

In summary, this study suggests that later age at menarche may be associated with increased SLE risk among black women. The few studies of age at menarche in relation to SLE risk are conflicting and a clear conclusion cannot be drawn. Results concerning long duration of breast feeding are conflicting as well. It appears that if reproductive factors are related to SLE, the associations are not strong enough to have clearly manifested across many studies to date.

Funding Support

Research reported in this publication was supported by the National Cancer Institute R01- CA058420, U01- CA164974; National Institute of Arthritis and Musculoskeletal and Skin Diseases R01 AR057327 and K24 AR066109; Dr. Barbhuiya is supported by the Rheumatology Research Foundation Scientist Development Award.

References

1. Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. *Arthritis Rheumatol* 2014;66:369–78. [PubMed: 24504809]
2. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. *Arthritis Rheum* 2013;65:753–63. [PubMed: 23203603]
3. McCarty DJ, Manzi S, Medsger TA Jr., Ramsey-Goldman R, LaPorte RE, Kwok CK. Incidence of systemic lupus erythematosus. Race and gender differences. *Arthritis Rheum* 1995;38:1260–70. [PubMed: 7575721]
4. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. *Arthritis Rheum* 2002;46:1830–9. [PubMed: 12124867]
5. Nagata C, Fujita S, Iwata H, et al. Systemic lupus erythematosus: a case-control epidemiologic study in Japan. *Int J Dermatol* 1995;34:333–7. [PubMed: 7607794]
6. Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007;56:1251–62. [PubMed: 17393454]
7. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. *J Am Med Womens Assoc (1972)* 1995;50:56–8. [PubMed: 7722208]
8. Russell C, Palmer JR, Adams-Campbell LL, Rosenberg L. Follow-up of a large cohort of Black women. *Am J Epidemiol* 2001;154:845–53. [PubMed: 11682367]
9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
10. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7. [PubMed: 7138600]
11. Parks CG, Miller FW, Satoh M, et al. Reproductive and hormonal risk factors for antinuclear antibodies (ANA) in a representative sample of U.S. women. *Cancer Epidemiol Biomarkers Prev* 2014;23:2492–502. [PubMed: 25086100]

12. Boynton-Jarrett R, Wright RJ, Putnam FW, et al. Childhood abuse and age at menarche. *J Adolesc Health* 2013;52:241–7. [PubMed: 23332491]
13. Wise LA, Palmer JR, Rothman EF, Rosenberg L. Childhood abuse and early menarche: findings from the black women’s health study. *Am J Public Health* 2009;99 Suppl 2:S460–6. [PubMed: 19443822]
14. Feldman CH, Malspeis S, Leatherwood C, Kubzansky L, Costenbader KH, Roberts AL. Association of Childhood Abuse with Incident Systemic Lupus Erythematosus in Adulthood in a Longitudinal Cohort of Women. *J Rheumatol* 2019;46:1589–96. [PubMed: 31092723]
15. Cozier YC, Barbhaiya M, Castro-Webb N, et al. Association of Child Abuse with Systemic Lupus Erythematosus in Black Women During Adulthood. *Arthritis Care Res (Hoboken)* 2020.
16. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 2005;17:271–301. [PubMed: 16761546]
17. Song GG, Lee YH. Circulating prolactin level in systemic lupus erythematosus and its correlation with disease activity: a meta-analysis. *Lupus* 2017;26:1260–8. [PubMed: 28420051]
18. Ledesma-Soto Y, Blanco-Favela F, Fuentes-Panana EM, et al. Increased levels of prolactin receptor expression correlate with the early onset of lupus symptoms and increased numbers of transitional-1 B cells after prolactin treatment. *BMC Immunol* 2012;13:11. [PubMed: 22404893]
19. Stuebe AM, Meltzer-Brody S, Pearson B, Pedersen C, Grewen K. Maternal neuroendocrine serum levels in exclusively breastfeeding mothers. *Breastfeed Med* 2015;10:197–202. [PubMed: 25831434]
20. Harris HR, Costenbader KH, Mu F, et al. Endometriosis and the risks of systemic lupus erythematosus and rheumatoid arthritis in the Nurses’ Health Study II. *Ann Rheum Dis* 2016;75:1279–84. [PubMed: 26238146]
21. Newburger EC, Curry A. Educational Attainment in the United States, March 1999 Current Population Reports: Washington, DC: U.S. Department of Commerce; 2000.

Figure 1.
Black Women's Health Study follow up flow chart, 1995–2015

Table 1.

Characteristics of SLE cases at diagnosis in the Black Women's Health Study (BWHS, n=125)

Lupus (ACR) Characteristics	Lupus cases (n=125)
Age at diagnosis $\pm$ SD years	43 $\pm$ 10
ANA positive	121 (97%)
Anti-dsDNA or Anti-Sm positive	61 (49%)
Anti-dsDNA only	37 (30%)
Anti-Sm only	10 (8%)
Anti-dsDNA and anti-Sm	14 (11%)
Arthritis	99 (79%)
Discoid rash	33 (26%)
Hematologic disorders	80 (64%)
Malar rash	39 (31%)
Neurologic disorders	13 (10%)
Oral Ulcer	23 (18%)
Photosensitivity	41 (33%)
Renal disorder	38 (30%)
Serositis	43 (34%)
Number ACR * criteria (of 11), mean $\pm$ SD	5.0 $\pm$ 1.2

ACR = American College of Rheumatology

dsDNA = double-stranded deoxyribonucleic acid

Sm = Smith

* Hochberg MC. Arthritis Rheum 1997;40:1725.

Table 2.Baseline Characteristics of the BWHS Cohort in 1995^{*}, n=58,243

	All BWHS (n=58,118) %	SLE Cases (n=125) %
<i>Population-based characteristics</i>		
Age, mean $\pm$ SD	39.0 $\pm$ 10.8	36.4 $\pm$ 9.4
BMI, kg/m ² , mean $\pm$ SD	28.0 $\pm$ 6.7	28.2 $\pm$ 8.2
Smoking		
Never	65	63
Past	19	19
Current	16	18
Alcohol Intake		
Never	56	65
Past	18	15
Current	25	21
<i>Childhood/Young Adulthood</i>		
BMI age 18 (, kg/m ² , mean $\pm$ SD	21.5 $\pm$ 4.1	22.0 $\pm$ 5.4
Parental Education, HS or less [*]	35	49
Passive smoking 0–10 years [*]	45	45
Age started smoking 14 years	4	5
Age started drinking 14 years	2	2
Age first OC 14 years	2	2
Ever childhood sexual abuse	4	12
Ever childhood physical abuse	23	29
<i>Reproductive factors</i>		
Age at Menarche 11 years	29	30
Parity		
nulliparous	35	36
1–2 births	45	49
3+ births	20	15
Age at first birth 25 years	59	54
Ever breastfeeding	40	40
Premenopausal	76	80
Ever Endometriosis	8	10
Birthweight (self): 2500–3999 grams [*]	27	29
Ever OC	76	73
Ever use of female hormone replacement therapy	15	19

^{*} All data reported at study baseline in 1995 except for parental education (2009), passive smoking (1997) and birthweight (1997).

Table 3.

Relation of Female Reproductive Factors to risk of systemic lupus erythematosus in the BWHS from 1995–2015, n=58,243

	<i>Cases</i>	<i>Person-years</i>	<i>Age- adjusted HR (95% CI)^a</i>	<i>Multivariable HR (95% CI)^b</i>
Age at menarche^c				
< 11	17	109830	1.43 (0.78, 2.60)	1.31 (0.72, 2.39)
11	20	160041	1.17 (0.66, 2.08)	1.12 (0.63, 1.99)
12	29	268018	1.00 (reference)	1.00 (reference)
13	27	230833	1.11 (0.66, 1.88)	1.12 (0.66, 1.90)
14	12	94153	1.23 (0.63, 2.41)	1.26 (0.64, 2.47)
15	20	87328	2.25 (1.27, 3.98)	2.31 (1.30, 4.11)
P for trend				0.08
Parity^d				
Nulliparous	44	263575	1.00 (reference)	1.00 (reference)
Parous	81	685852	0.86 (0.58, 1.28)	0.93 (0.63, 1.38)
1 birth	36	236352	1.05 (0.67, 1.64)	1.12 (0.71, 1.76)
2 births	26	244597	0.76 (0.46, 1.26)	0.82 (0.50, 1.38)
3 births	11	122042	0.67 (0.34, 1.32)	0.72 (0.36, 1.44)
4 births	8	82862	0.79 (0.36, 1.74)	0.84 (0.38, 1.87)
Age at first birth^d				
Nulliparous	44	263575	1.00 (reference)	1.00 (reference)
< 25 years	46	429530	0.78 (0.50, 1.21)	0.89 (0.56, 1.44)
25–29 years	20	141259	1.02 (0.59, 1.75)	1.13 (0.65, 1.96)
30 years	14	102987	1.04 (0.56, 1.93)	1.09 (0.58, 2.05)
Lactation^{de}				
Never	42	358919	1.00 (reference)	1.00 (reference)
Ever	38	323652	1.12 (0.72, 1.76)	1.17 (0.74, 1.85)
< 6 months	14	176987	0.76 (0.41, 1.40)	0.78 (0.42, 1.45)
6 months	24	146665	1.58 (0.94, 2.65)	1.73 (1.01, 2.94)
Menopausal status^d				
Premenopausal	93	509187	1.00 (reference)	1.00 (reference)
Hysterectomy	10	129858	0.62 (0.29, 1.32)	0.57 (0.26, 1.24)
Postmenopausal	20	275591	0.73 (0.36, 1.51)	0.62 (0.29, 1.32)
age < 40	3	48884	0.47 (0.14, 1.57)	0.37 (0.11, 1.30)
age 40–44	6	43296	1.27 (0.49, 3.32)	1.07 (0.39, 2.89)
age 45	9	174267	0.53 (0.20, 1.38)	0.48 (0.18, 1.25)
age unknown	2	9145	1.93 (0.45, 8.28)	1.68 (0.39, 7.34)
Endometriosis^d				
Never	111	861661	1.00 (reference)	1.00 (reference)
Ever	14	92814	1.28 (0.73, 2.25)	1.27 (0.72, 2.25)

^a All models were adjusted for age and period

^{b,c} Age at menarche was adjusted for age started smoking 14 years, age started alcohol intake 14 years, age first OC 14 years, BMI at age 18, parental education, ever child sexual abuse, and ever child physical abuse.

^{b,d} Parity, age at first birth, lactation, menopause, and endometriosis were adjusted for alcohol status, smoking status, BMI, BMI at age 18, parity(except parity), menopausal status (except menopause), current OC use, ever use of female hormone, age at menarche.

^e Restricted to parous women. We used an indicator variable of having three or more births against having less than three births to control for parity.