Reproductive Factors and Risk of Systemic Lupus Erythematosus: Nationwide Cohort Study in Denmark

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ABSTRACT. ***Objective.*** The female predominance in systemic lupus erythematosus (SLE) suggests the possible involvement of reproductive factors in its etiology. We evaluated the relationship between parity and pregnancy losses and subsequent risk of SLE in a population-based cohort study.

Methods. We followed 4.4 million Danes aged 15–69 years for first inpatient hospitalizations for SLE between 1977 and 2004. As measures of relative risk, we used Poisson regression-derived hospitalization rate ratios (RR) with 95% confidence intervals (CI) for cohort members with different reproductive histories.

Results. Overall, 1614 women and 274 men were hospitalized with SLE during 88.9 million person-years of followup. Number of children was unrelated to SLE risk in men, but women with at least one liveborn child were at lower risk than nulliparous women (RR 0.74; 95% CI 0.64–0.86), and women with 2 or more children were at lower risk than 1-child mothers. Recurrent idiopathic pregnancy losses, including spontaneous abortions, missed abortions, and stillbirths, were associated with markedly increased SLE risk (RR 3.50; 95% CI 2.38–4.96, for 2+ vs none; $p < 0.001$).

Conclusion. Nulliparous women, 1-child mothers, and women who experience spontaneous abortions, missed abortions, or stillbirths are at increased SLE risk. Theoretically, immunological processes involved in subfertility or idiopathic pregnancy losses might act as initiating or contributing factors in some cases of SLE. However, considering the well established excess of pregnancy complications in women with established SLE, the observed associations more likely reflect the effect of subclinical immunological processes in women destined to develop SLE. (First Release July 1 2009; J Rheumatol 2009;36:1903–9; doi:10.3899/jrheum.090002)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is an autoimmune, multisystem connective tissue disorder, in which patients may exhibit a broad range of clinical presentations. Symptoms may range from nonspecific presentations, such as fatigue, oral ulcers, and photosensitive skin, to a life-threatening condition when vital organs are affected[1]. Serologically, SLE is characterized by the circulation of a wide variety of autoantibodies, among which antinuclear antibodies, primarily anti-double-stranded-DNA[2], may be present many years before clinical onset[3].

The reported strong female predominance in SLE with female:male ratios ranging from 4.3 to 13.6[4] and the typical age of onset during and shortly after childbearing years suggest that reproductive factors might somehow be etiologically involved. However, while a marked excess of pregnancy complications has been established for women with clinical SLE[5,6], findings regarding the possible association between menstrual and childbearing variables and subsequent risk of SLE have generally been inconsistent. Young age at menarche was associated with increased risk of SLE in one study[7], decreased risk in another[8], while still other studies found no association[9-11]. Similarly, early natural menopause and surgical menopause were related to an increased risk of SLE in some studies[7,10], but not in others[9,11]. Studies on the possible role of childbearing and pregnancy losses in relation to SLE risk have generally been negative[7,9-11], but one recent study reported a statistically significant association between adverse pregnancy outcomes and increased risk of SLE[12]. Overall, current research does not provide any conclusive evidence regarding the possible role of reproductive factors in the etiology of SLE.

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The aim of our study was to undertake a statistically powerful, population-based assessment of associations between a number of reproductive factors and subsequent SLE risk in persons without a known record of the disease. We conducted a cohort study based on reproduction and health registries covering the entire population in Denmark. The analysis of the possible effect of children was performed for both women and men. This was done to allow a better distinction between the possible physiological effects of pregnancy (which apply to women) and socioeconomic or other factors associated with childbearing patterns (which may apply to both women and men).

MATERIALS AND METHODS

Study cohort. The cohort consisted of 4.4 million women and men born between 1935 and 1989. Cohort members were identified through the Civil Registration System, a continuously updated national demographic database in operation since 1968[13]. By means of the unique 10-digit identification number assigned to all Danish residents, the cohort was linked to national reproduction and health registries to obtain information about reproductive histories and subsequent first hospitalizations for SLE.

Reproductive history. For both women and men, information about children was available in the Civil Registration System[13]. For each cohort member, the number of children was operationally defined as the number of pregnancies that resulted in at least 1 liveborn child. For women born 1955 or later, we also evaluated the possible effect of iatrogenic pregnancy terminations and idiopathic pregnancy losses. Specifically, we obtained detailed information about induced abortions [International Classification of Diseases (ICD-8) codes 640, 641, 642 and ICD-10 codes O04, O05, O06] from the National Registry of Induced Abortions[14] and the Danish National Patient Registry[15] (period: January 1974 through December 2004). For ectopic pregnancies (ICD-8 code 631 and ICD-10 code O00), spontaneous abortions (ICD-8 code 643 and ICD-10 code O03), missed abortions (ICD-8 codes 63461, 63462, 63463, 63469, 6451, and ICD-10 code O021), and hydatidiform moles (ICD-8 codes 63429, 6450, and ICD-10 code O01), we used data from the Danish National Patient Registry (period: January 1977 through December 2004). Data about stillbirths were obtained from the Medical Birth Registry[16] and the Danish National Patient Registry (period: January 1973 through December 2004).

SLE diagnoses. As in other recent large-scale studies on the epidemiology of SLE and other autoimmune diseases[17-22], we obtained information in the Danish National Patient Registry about first inpatient hospital contacts with a recorded diagnosis of SLE in the cohort from January 1977 through December 2004 (ICD-8 code 73419 and ICD-10 group M32).

Stratification of person-years and SLE outcomes. We analyzed data for women and men separately. Each cohort member contributed person-years at risk from her or his 15th birthday or January 1, 1977, whichever came later (January 1, 1977, is the date of the start of the Danish National Patient Registry) and until the date of first inpatient hospital contact with a diagnosis of SLE, death, emigration, or January 1, 2005, whichever came first. We considered only pregnancies occurring before the first hospitalization for SLE as potential risk factors. Person-years and SLE outcomes were stratified in a time-dependent manner according to age (1-yr age groups), calendar period (5-yr groups), marital status (unmarried, married, separated/divorced, widowed), and each of the following live birth-related variables: number of children (0, 1, 2, 3, 4+), age at birth of first child (< 20, 20-24, 25-29, 30+ yrs), and time since birth of most recent child (< 5, 5-9, 10-14, 15-19, 20+ yrs). For women born 1955 or later, we also stratified person-years and SLE outcomes by the number of induced abortions (0, 1, 2+), ectopic pregnancies (0, 1+), hydatidiform moles (0, 1+), spontaneous abortions (0, 1+), missed abortions (0, 1+), and stillbirths (0, 1+), the number of idiopathic pregnancy losses, a combined variable including spontaneous abortions, missed abortions, and stillbirths (0, 1, 2+), as well as by the time since the most recent idiopathic pregnancy loss (< 1, 1-2, 3-4, 5-9, 10-14, 15-19, 20+ yrs).

Poisson regression analysis. The statistical analysis of the resulting table of stratum-specific SLE hospitalization rates was a log-linear Poisson regression analysis carried out by the GENMOD procedure in SAS version 9.1. Resulting ratios of first inpatient hospitalization rates (RR) for SLE with 95% confidence intervals (CI) served as measures of relative risk. In RR calculations, we adjusted for age using cubic splines restricted to be linear in the tails[23], while adjustment for calendar period, marital status, and other variables was performed using the categorizations described above. In trend tests, categorized quantitative variables were treated as continuous variables by replacing each category by the person-years-weighted median of the original variable in that category. Trend tests were carried out only after acceptance ($p \geq 0.05$) of the corresponding model reduction from a categorical to a linear description of the association between SLE and the variable in question. Throughout, p values less than 0.05 (2-sided) and 95% CI excluding unity were considered indicators of statistical significance.

Ethics. The study involved no patient contact and was approved (approval no. 2008-41-2374) by the Danish Data Protection Agency.

RESULTS

Women. In the cohort of 2.14 million women born between 1935 and 1989, a total of 1614 cases of SLE occurred during 43.6 million person-years of followup between 1977 and 2004. The median age at first inpatient hospitalization for SLE was 36 years (range 15–69 yrs). A number of statistically significant associations were observed between women's reproductive histories and their subsequent SLE risk.

Compared with nulliparous women, women with 1 or more children were at 26% reduced risk of SLE (RR 0.74; 95% CI 0.64–0.86), and the risk dropped even more for women with 2 or more children (Table 1). However, a direct, linear association with increasing number of children was not apparent, as the SLE risk did not decline further among women with more than 2 children.

There was an inverse, linear relationship between the age at which a woman gave birth to her first child and her subsequent risk of SLE (p trend < 0.001). Indeed, compared with the reference group of women who had their first child at age 20–24 years, the risk of SLE was significantly lower in women whose first child was born at age 25–29 years (RR 0.76; 95% CI 0.65–0.89) or at age 30 years or later (RR 0.69; 95% CI 0.54–0.88) (p trend < 0.001) after adjusting for age, calendar period, marital status, and number of children. A statistically significant trend was also observed for the association between the time since birth of the most recent child and SLE risk. The shorter the interval since the most recent childbirth, the lower was the risk of SLE (p trend < 0.001) after adjusting for age, calendar period, marital status, number of children, and age at birth of first child.

Information about adverse pregnancy outcomes was available for women born between 1955 and 1989. In this analysis of 1.39 million women followed for 23.6 million person-years, a total of 737 cases of SLE occurred between

Table 1. Rate ratios (RR) of systemic lupus erythematosus (SLE) according to live birth history among 15 to 69-year-old Danish women and men. Analysis of the effects of live births was carried out for a cohort of 2,140,056 women and 2,243,840 men born 1935 through 1989 who were 15–69 years old during followup for SLE in the period 1977 through 2004.

	Women				Men			
	SLE Cases	Person-yrs	RR*	95% CI	SLE Cases	Person-yrs	RR*	95% CI
Children**								
0	560	16,648,004	1	Reference	96	21,965,076	1	Reference
1+	1054	26,903,931	0.74	0.64–0.86	178	23,339,186	0.84	0.59–1.21
No. of children								
1	324	7,086,195	1	Reference	38	6,519,928	1	Reference
2	480	12,989,303	0.68	0.58–0.79	92	11,062,771	1.08	0.74–1.62
3	181	5,142,310	0.58	0.48–0.71	36	4,298,889	0.93	0.58–1.51
4+	69	1,686,123	0.64	0.48–0.83	12	1,457,598	0.84	0.41–1.60
Test for homogeneity				p < 0.001				p = 0.79
Trend test				NA				p = 0.52
Age at birth of first child, yrs								
< 20	208	4,510,501	1.16	0.99–1.37	4	1,052,996	0.42	0.13–1.01
20–24	522	12,720,039	1	Reference	82	8,440,800	1	Reference
25–29	244	7,345,547	0.76	0.65–0.89	66	9,320,202	0.73	0.52–1.01
30+	80	2,327,844	0.69	0.54–0.88	26	4,525,187	0.58	0.36–0.91
Test for homogeneity				p < 0.001				p = 0.03
Trend test				p < 0.001				p = 0.08
Time since birth of most recent child, yrs								
< 5	217	7,603,814	0.62	0.49–0.77	25	7,343,081	0.74	0.41–1.36
5–9	168	4,802,960	0.73	0.58–0.90	39	4,533,481	1.49	0.89–2.54
10–14	191	4,071,780	1	Reference	24	3,633,576	1	Reference
15–19	157	3,499,960	1.02	0.82–1.27	22	2,916,360	1.02	0.56–1.85
20+	321	6,925,418	1.15	0.91–1.46	68	4,912,688	1.39	0.80–2.49
Test for homogeneity				p < 0.001				p = 0.06
Trend test				p < 0.001				p = 0.18

* All RR are adjusted for age, calendar period, and marital status. In addition, RR for number of children and age at birth of first child are mutually adjusted for each other; RR for time since birth of most recent child are adjusted for number of children and age at birth of first child. ** Number of children operationally defined as each woman's number of pregnancies that resulted in at least 1 liveborn child and among men as the number of pregnancies they fathered that resulted in at least 1 liveborn child. NA: not applicable.

1977 and 2004 at a median age of 27 years (range 15–49 yrs). For each of the 3 types of idiopathic pregnancy losses we studied, including spontaneous abortion, missed abortion, and stillbirth, there was a statistically significant relationship with increased SLE risk after adjusting for potential confounding by age, calendar period, marital status, number of children, and age at birth of first child (Table 2). Specifically, compared with women without a history of the idiopathic pregnancy loss in question, women who had experienced at least 1 spontaneous abortion were at a 43% higher risk of SLE (RR 1.43; 95% CI 1.08–1.88), women who had had 1 or more missed abortions were at an approximately doubled risk (RR 2.13; 95% CI 1.48–2.98), and women with 1 or more stillbirths were at an almost 4 times increased risk of SLE (RR 3.93; 95% CI 1.95–6.96). Considering the 3 types of idiopathic pregnancy losses together, women who had experienced 2 or more idiopathic pregnancy losses were at a more than tripled risk of SLE compared with women without such pregnancy losses (RR 3.50; 95% CI 2.38–4.96). The risk of SLE was approximately 2-fold elevated in the first 5 years after the most recent idiopathic pregnancy loss and decreased significantly thereafter (RR 2.64; 95% CI 1.18–6.29, for < 1 vs 10–14 yrs after the most recent idiopathic pregnancy loss; p trend = 0.008). In a supplementary analysis of the association between idiopathic pregnancy losses and SLE risk, we restricted the focus to those idiopathic pregnancy losses that preceded the first hospitalization for SLE by at least 5 years. In this analysis, the increased risk of SLE following 2 or more idiopathic pregnancy losses remained statistically significant (RR 2.11; 95% CI 1.12–3.61, for > 2 vs no idiopathic pregnancy losses, n = 12 cases of SLE). Induced abortions, ectopic pregnancies, and hydatidiform moles were not associated with altered risk of SLE.

Having observed statistically significant associations between idiopathic pregnancy losses and SLE risk, we examined if the inverse associations observed in Table 1 between live births and SLE might be due to confounding by a lower prevalence of idiopathic pregnancy losses among parous women. Specifically, we repeated the analysis in

Table 2. Rate ratios (RR) of systemic lupus erythematosus (SLE) according to history of pregnancy losses among Danish women 15 to 49 years old. Analysis of the effects of pregnancy losses were carried out for a cohort of 1,387,186 women born 1955 through 1989 who were 15–49 years old during followup for SLE in the period 1977 through 2004.

	SLE Cases	Person-yrs	RR*	95% CI
Spontaneous abortion				
0	678	22,358,387	1	Reference
1+	59	1,222,995	1.43	1.08–1.88
Missed abortion				
0	702	23,090,719	1	Reference
1+	35	490,663	2.13	1.48–2.98
Stillbirth				
0	727	23,508,586	1	Reference
1+	10	72,796	3.93	1.96–6.96
Any idiopathic pregnancy loss**				
0	651	21,917,110	1	Reference
1	54	1,382,860	1.21	0.90–1.61
2+	32	281,412	3.50	2.38–4.96
Test for homogeneity				$p < 0.001$
Trend test				NA
Time since most recent idiopathic pregnancy loss, yrs				
< 1	16	180,686	2.64	1.18–6.29
1–2	18	305,309	1.90	0.87–4.48
3–4	16	257,888	2.05	0.92–4.88
5–9	20	474,480	1.37	0.64–3.17
10–14	9	269,905	1	Reference
15–19	5	125,382	1.09	0.33–3.17
20+	2	50,622	1.01	0.15–3.98
Test for homogeneity				$p = 0.21$
Trend test				$p = 0.008$
Induced abortion				
0	590	19,731,810	1	Reference
1	111	2,855,554	1.18	0.95–1.45
2+	36	994,018	1.08	0.75–1.51
Test for homogeneity				$p = 0.30$
Trend test				$p = 0.23$
Ectopic pregnancy				
0	724	23,256,735	1	Reference
1+	13	324,647	1.06	0.58–1.77
Hydatidiform mole				
0	736	23,555,389	1	Reference
1+	1	25,993	1.09	0.06–4.80

* All RR are adjusted for age, calendar period, marital status, number of children, and age at birth of first child.
** Spontaneous abortion, missed abortion, or stillbirth.

Table 1, this time restricting the analysis to women born 1955-1989, the subcohort for whom we had information available about adverse pregnancy outcomes. RR estimates for all live birth variables shown in Table 1 were virtually identical in this younger subset of the cohort, whether or not the RR were adjusted for history of idiopathic pregnancy losses (data not shown).

Men. In the cohort of 2.24 million men born between 1935 and 1989, a total of 274 cases of SLE occurred during 45.3 million person-years of followup. The median age at first inpatient hospitalization for SLE was 41 years (range 15–69 yrs). After adjusting for age, calendar period, and marital status there was no statistically significant relationship between a man's number of children or the time interval since the birth of his most recent child and his subsequent risk of SLE (Table 1). However, as for women, the risk of SLE among men who were age 30 years or older at the birth of their first child was significantly reduced compared with men who had their first child at age 20–24 years (RR 0.58; 95% CI 0.36–0.91).

DISCUSSION

To our knowledge, this study is by far the largest to address possible associations between reproductive factors and subsequent risk of SLE. With 1614 cases of SLE occurring in our cohort of women and 274 cases in men during a total of

88.9 million person-years of followup, the statistical power to detect even modest changes in SLE risk as statistically significant clearly exceeds that of prior studies. The salient observations in our study were increased risks of SLE in nulliparous women, 1-child mothers, and women who experience idiopathic pregnancy losses.

Our study benefited from the favorable opportunities for the conduct of population-based cohort studies in Denmark[24] because each citizen's unique personal identification number is used in the organization of all administrative and health-related records in the country. We followed a cohort comprising all Danish residents born between 1935 and 1989 and identified their recorded reproductive histories and subsequent inpatient hospitalizations for SLE in national registries. Thus, by design our cohort study is free of possible selection biases that may complicate interpretation of findings in case-control studies. Further, our study is the first to carry out parallel analyses of the possible effect of children in both women and men, an approach that helps distinguish between pregnancy-related and other explanations of the observed associations in women.

It is well known that women with already established SLE are at an elevated risk of complications in the event of pregnancy[5,6]. Complications include higher risks of cesarean section, preterm labor, intrauterine growth restriction, preeclampsia, eclampsia, spontaneous abortion, and stillbirth[6,25,26]. The risk of pregnancy complications in patients with SLE is influenced by numerous risk factors pertaining to the course of the disease itself, including the presence of flares, lupus nephritis, hypertension, and antiphospholipid antibodies[5,25]. It has been estimated that around 20% of pregnancies in patients with SLE result in pregnancy loss[25].

From an etiological point of view the possible association between pregnancies and subsequent risk of SLE in healthy individuals is less clear. So far, studies that have investigated the association between parity and risk of SLE have failed to find a significant relationship[7-11]. Similarly, 1 study reported no relationship between the age at first childbirth and subsequent risk of SLE[7]. This stands in contrast with observations in our study, which showed a statistically significant relationship between parity and the risk of SLE, with highest risk among nulliparous women, lowest risk among women with 2 or more children, and a significant trend of decreasing SLE risk with increasing age at first child.

Regarding the possible role of pregnancy complications, one recent study indicated a relationship between stillbirths, preterm births, growth restriction, and low birth weight and an increased risk of subsequent SLE[12]. The authors suggested that poor fetal outcomes might be indicative of a predisease state where subclinical SLE complicates pregnancies before the disease itself becomes clinically apparent. This is in accord with our finding that idiopathic pregnancy losses were followed by significantly increased risk of SLE, most notably in the first 5 years after the pregnancy loss. However, findings in other studies do not support an association between pregnancy losses and risk of SLE[9,11]. To our knowledge no prior study has investigated the possible role of induced abortions, ectopic pregnancies, or hydatidiform moles in relation to subsequent risk of SLE. Our study found no influence from these variables, which indicates that it is not the pregnancy termination as such that is linked to increased SLE risk. Rather, the underlying immunological abnormalities that result in spontaneous abortion, missed abortion, or stillbirth seem to be responsible.

An unknown proportion of the pregnancy losses that we observed in women who later developed SLE may have occurred before the first immunological changes in SLE pathogenesis. Theoretically, such pregnancy losses might therefore be considered as potential immunological triggers in the etiology of SLE. On the other hand, because the first symptoms precede the diagnosis by, on average, 5.7 years in Danish patients with SLE[27], a substantial part of the reproductive period in those of our cohort members who were eventually hospitalized with SLE likely took place in a predisease state when the immunological processes leading to SLE had already started. In these situations, pregnancy losses may have served as cofactors in SLE pathogenesis if adverse pregnancies somehow potentiated the cascade of immunological processes already in progress. However, in light of the well documented excess of pregnancy complications in patients with established SLE[5,6], the finding of SLE-related immunological changes several years before diagnosis[3], and the excess risk of SLE within 5 years after the most recent idiopathic pregnancy loss in our study, it appears more likely that the observed inverse association with live births and the positive association with idiopathic pregnancy losses would be due to subclinical immunological changes that lead to increased rates of nulliparity and idiopathic pregnancy losses in women already destined to develop SLE. Unfortunately, we did not have access to prospectively collected serum samples that would permit a clear distinction between these alternative interpretations. However, one thing can be concluded from our findings: the well known excess of pregnancy complications in patients with SLE is present at markedly increased rates even before the first hospital visit for SLE. Regardless of the underlying mechanism, nulliparous women and women who experience idiopathic pregnancy losses, especially recurrent pregnancy losses, seem to be a high-risk group for SLE.

Our study has a number of limitations that need attention. As in other large-scale epidemiologic studies, we relied on routinely collected register data, so the information about reproductive variables and SLE outcomes in our study needs consideration. While records of live births, stillbirths, and induced abortions in Danish registers are likely to be accurate and virtually complete, the validity and completeness of other reproductive variables are likely to be lower. As seen

in a recent cohort study of 11,088 Danish women, a non-negligible proportion of spontaneous abortions will never appear in hospitalization records. Specifically, of 654 spontaneous abortions reported by these women who knew they were pregnant, some 459 (70%) could be traced under codes for spontaneous abortion in the files of the Danish National Patient Register[28]. It is reassuring, therefore, that our statistically significant findings for each of the 3 types of idiopathic pregnancy losses occurred despite the possible influence of unspecified data errors and underascertainment that would tend to favor null findings. Also, the registry information we used to identify patients with SLE in our cohort is likely to be reasonably accurate and has been used in previous studies[17,19,20]. Specifically, 76% of women and 72% of men who were treated as SLE inpatients in Denmark during the study period had at least one subsequent hospital contact with a record of SLE in either ambulatory settings or as inpatients, suggesting that most SLE diagnoses were accurately recorded. In a previous study of the SLE incidence in a demographically representative sample of the Danish population, other researchers showed that of 104 patients with SLE who were alive at the time of study, all had been diagnosed and/or received treatment in a hospital setting, and most patients had been treated as inpatients at some point[28]. Consequently, by using inpatient hospitalization records to define SLE outcomes in our study, we likely identified the majority of patients with SLE treated in Denmark during the study period. Nevertheless, our findings may not necessarily apply to milder cases of SLE treated exclusively in outpatient settings.

We used ratios of first hospitalization rates as our measure of relative risk of SLE for persons with different reproductive histories. Ideally, comparisons should be carried out using dates of SLE diagnosis in the patients, not their first hospitalization dates. However, diagnoses of SLE can be difficult to establish, and diagnostic criteria may accumulate over several years, thus making it difficult to define the time of diagnosis from routine hospital records. In light of these diagnostic challenges, which apply to SLE and several other autoimmune diseases, we and others have previously used hospitalization rate ratios as reasonable measures of relative risk in studies of SLE and other autoimmune diseases[17,18,20-22].

The finding of higher risk of SLE among nulliparous women and 1-child mothers and, among parous women, of a significant inverse association between age at first childbirth and SLE risk, may indirectly reflect that childbearing women tend to be healthy around the time of pregnancy. In any given age group, women who become pregnant and deliver a live born child are likely to comprise a higher proportion of healthy women than the complementary group of same-aged women without children. This marker function of good health likely becomes stronger with age, simply because women who become pregnant at more advanced ages do so only because they have stayed free of diseases and conditions that reduce their fecundability. In other words, the ability to conceive and give birth to a live-born child may be a stronger marker of the absence of major immune-mediated morbidity that might interfere with normal reproduction in women aged 30 years or older than in women younger than 20 years.

We had only a few variables available to control for potential confounding by socioeconomic or lifestyle factors. Specifically, we adjusted for marital status, but other potential confounders such as tobacco smoking, which is a risk factor for SLE[8,29,30], may have affected the observed risk associations between reproductive factors and SLE risk. To partially overcome this limitation, we carried out all analyses of the effect of live births in both women and men. For men, fatherhood histories were generally unrelated to SLE risk except for a reduced risk in men who were age 30 years or older at the birth of their first child. As with women, the ability of a man to have children at a relatively advanced age may serve as a marker of freedom from underlying immunological disease. Alternatively, socioeconomic differences that we were unable to adjust for might explain the lower risk of SLE in men and women who had their first child at or after age 30 years. However, since we found statistically significant associations with nulliparity, 1-child parenthood, and time since the birth of the most recent child only among women, it seems likely that the underlying mechanisms in women are truly related to biological aspects of pregnancy.

With due reservations, our study shows that nulliparous women, 1-child mothers, and women who experience idiopathic pregnancy losses are at increased risk of SLE, notably women with a history of recurrent idiopathic pregnancy losses. Whether a true causal relationship exists between nulliparity and idiopathic pregnancy losses and some cases of SLE cannot be concluded from our study. However, given the long subclinical phase in some patients with SLE and the well described excess of pregnancy complications in women with established clinical SLE, it seems likely that subclinical immunological changes in women destined to develop SLE may be the major explanation of our findings. Regardless of the underlying mechanism, our study shows that the excess of pregnancy complications in women with SLE is not limited to the time after diagnosis.

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