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Childbearing and the Risk of Scleroderma: A Population-based Study in Sweden

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This study examined associations between childbearing and risk of scleroderma by using national population-based registry data from Sweden. Women with a discharge diagnosis of scleroderma from 1964 to 1999 (n = 2,149) were identified in the Swedish Inpatient Register. These cases were matched by year and month of birth and region of residence to as many as five controls obtained from the Multi-Generation Register. Pregnancy history (number of births, age at each birth) was restricted to births before the first scleroderma-related hospitalization for cases and the corresponding age for their matched controls. Risk estimates, measured by the odds ratio and 95% confidence interval, were obtained by using conditional logistic regression. Nulliparity was associated with an increased risk of scleroderma (odds ratio = 1.37, 95% confidence interval: 1.22, 1.55). Risk decreased with increasing number of births. Similar results were found when analyses were limited to births up to 2 years or up to 5 years before hospitalization. Among parous women, younger age at first birth was associated with an increased risk of scleroderma. The association between lower parity and increased risk of scleroderma could reflect subfecundity caused by scleroderma before disease became clinically evident, possible common causes of infertility and scleroderma, or a protective effect of pregnancy through an unknown mechanism.

maternal-fetal exchange; parity; pregnancy; scleroderma, systemic

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; OR, odds ratio.

Scleroderma (systemic sclerosis) is a severe autoimmune connective tissue disease characterized by fibrosis and vascular lesions affecting large and small blood vessels and other organs. The skin, lungs, heart, kidneys, and gut are primary sites of damage and resulting complications of the disease (1). It is relatively rare (incidence: 1–2 per 100,000 person-years) but is associated with significant mortality, with a median survival time of approximately 11 years. Scleroderma disproportionately affects women (85–90 percent of patients are female) (2, 3). Occupational exposure to crystalline silica (4) and solvents (5) has been associated with this disease, but its etiology and the reasons for the excess risk among women are not known.

Because the incidence of scleroderma peaks after childbearing years, it has been proposed that hormonal factors or exposure to persisting fetal cells in maternal blood following pregnancy—microchimerism—is involved in its pathogenesis (6, 7). The latter hypothesis has been supported by laboratory findings showing that fetal cells in maternal sera were more common in parous women with scleroderma than in healthy controls (8). However, evidence for childbearing as an etiologic factor or risk modifier of scleroderma risk is limited. One recent epidemiologic study assessed the role of parity in the development of scleroderma (9). In that small case-control study, nulliparity was associated with an increased risk of developing scleroderma. The objective of the present study was to examine possible associations between childbearing and the risk of scleroderma by using population-based registry data.

MATERIALS AND METHODS

The Swedish Multi-Generation Register

The Swedish Multi-Generation Register includes index persons born in 1932 or later who were alive in 1961, with

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links to their parents, siblings, and offspring. In 2000, the database encompassed almost 11 million persons identifiable by a unique national registration number assigned to all Swedish residents. The database has been used extensively in epidemiologic research to assess familial cancer risks (10).

The Swedish Inpatient Register

The Swedish Inpatient Register, established in 1964 and with complete national coverage from 1987 onward, includes data on individual hospital discharges. Each record corresponds to one hospital admission and contains, in addition to the patient's national registration number, the dates of admission and discharge, with diagnoses coded according to *International Classification of Diseases* (ICD), Seventh Revision (ICD-7, 1964–1968); Eighth Revision (ICD-8, 1969–1986); Ninth Revision (ICD-9, 1987–1996); and Tenth Revision (ICD-10, 1997–1999). The primary and as many as eight additional diagnoses are recorded for each hospitalization; specifically used in this study were ICD-7 codes 710.05, 710.06, 710.07, and 710.09; ICD-8 codes 701.00, 734.00, 734.01, and 734.09; ICD-9 codes 701A and 710B; and ICD-10 codes M340, M341, M348, and M349.

For the present study, the national registration number was used to link women in the Inpatient Register who had a first discharge diagnosis (primary or secondary) of scleroderma between 1964 and 1999 to the Multi-Generation Register (11), obtaining for each case information on reproductive history (number of births, including nulliparity, and age at births). For every case, up to five controls, matched on month and year of birth and region of residence, were randomly selected from women in a National Population Register who were alive at the case's diagnosis date, without themselves having been diagnosed with scleroderma. Reproductive data for controls were obtained in the same manner as that for cases. The randomly chosen controls were used only once. Pregnancy data were limited to pregnancies ending before the first scleroderma-related hospitalization date for each case and her corresponding controls. The analyses were restricted to women born in 1917 or later to ensure that the reproductive period was fully covered by information available in the Multi-Generation Register. In this manner, 2,149 women with a discharge diagnosis of scleroderma and 9,879 controls were available for analysis.

We used conditional logistic regression to estimate the odds ratios and 95 percent confidence intervals as measures of association between parity, age at first birth, and risk of scleroderma. The analyses were conducted by using the SAS statistical package (SAS Institute, Inc., Cary, North Carolina).

The study was approved by the Institutional Review Board of Karolinska Institutet, Stockholm.

RESULTS

Table 1 shows the characteristics of scleroderma patients and their matched controls. Median age at first hospitalization for scleroderma was 54 years, with one third of the cases being aged 60 years or older. Twenty-four percent of cases and 19 percent of controls were nulliparous. Compared with parous women, childless women were at an increased risk of scleroderma (odds ratio (OR) = 1.37, 95 percent confidence interval (CI): 1.22, 1.55) (table 2). Results were similar when analyses were restricted to births up to 2 years (OR for nulliparity = 1.36, 95 percent CI: 1.20, 1.54) or up to 5 years (OR for nulliparity = 1.32, 95 percent CI: 1.16, 1.49) before hospitalization. An increased risk for nulliparous women remained when the analysis was restricted to hospital discharges between 1987 and 1999 (ICD-9 and ICD-10) (OR = 1.25, 95 percent CI: 1.05, 1.48) or to primary diagnoses only (OR = 1.22, 95 percent CI: 1.02, 1.46).

Among parous women, there was a monotonic decrease in risk with increasing parity (table 2). When nulliparous women were used as the comparison group, the odds ratios

TABLE 1. Characteristics of scleroderma cases at time of first hospitalization and of their matched controls, Sweden, 1964–1999

	Cases (n = 2,149)		Controls* (n = 9,879)	
	No.	%	No.	%
Age (years)				
16–29	145	7	677	7
30–39	213	10	961	10
40–44	189	9	866	9
45–49	228	11	1,030	10
50–54	301	14	1,390	14
55–59	352	16	1,637	17
≥60	721	34	3,318	34
Year (ICD† version)				
1964–1968 (ICD-7)	26	1		
1969–1986 (ICD-8)	962	45		
1987–1996 (ICD-9)	765	36		
1997–1999 (ICD-10)	396	18		
No. of births				
0	509	24	1,898	19
1	450	21	1,929	20
2	690	32	3,390	34
3	328	15	1,696	17
4	112	5	615	6
≥5	60	3	351	4
Age at first birth (years)‡				
<20	222	14	864	11
20–24	658	40	3,319	42
25–29	519	32	2,626	33
30–34	186	11	871	11
≥35	55	3	301	4

* As many as five controls were matched to each case by year and month of birth and region of residence.

† *International Classification of Diseases* (ICD), Seventh Revision (ICD-7), Eighth Revision (ICD-8), Ninth Revision (ICD-9), Tenth Revision (ICD-10).

‡ Among parous women.

TABLE 2. Associations among parity, age at first birth, and risk of scleroderma among patients hospitalized for scleroderma, Sweden, 1964–1999*

	Full sample (2,149 cases, 9,879 controls)		Age <45 years (547 cases, 2,504 controls)		Age ≥45 years (1,602 cases, 7,375 controls)	
	OR†	95% CI†	OR	95% CI	OR	95% CI
Parity up to time of hospitalization						
0	1.37	1.22, 1.55	1.60	1.26, 2.03	1.30	1.13, 1.50
≥1	1.0	Referent	1.0	Referent	1.0	Referent
0	1.0	Referent	1.0	Referent	1.0	Referent
1	0.84	0.73, 0.98	0.76	0.57, 1.02	0.88	0.74, 1.05
2	0.71	0.62, 0.82	0.60	0.46, 0.79	0.75	0.64, 0.88
3	0.68	0.57, 0.80	0.52	0.37, 0.75	0.73	0.60, 0.88
4	0.60	0.47, 0.77	0.42	0.23, 0.77	0.66	0.50, 0.86
≥5	0.58	0.43, 0.79	0.15	0.04, 0.65	0.67	0.49, 0.92
p for trend	<0.01		<0.01		<0.01	
Nulliparous up to 2 years before hospitalization	1.36	1.20, 1.54	1.54	1.21, 1.95	1.30	1.13, 1.50
Nulliparous up to 5 years before hospitalization	1.32	1.16, 1.49	1.37	1.07, 1.75	1.30	1.13, 1.50
Age (years) at first birth‡ per year increase	0.982	0.969, 0.995	0.966	0.935, 0.998	0.985	0.971, 0.999
13–19	1.0	Referent	1.0	Referent	1.0	Referent
20–24	0.77	0.64, 0.92	0.93	0.65, 1.32	0.72	0.58, 0.89
25–29	0.77	0.64, 0.93	0.76	0.52, 1.13	0.76	0.61, 0.95
30–34	0.86	0.68, 1.09	0.85	0.50, 1.43	0.86	0.66, 1.10
≥35	0.70	0.50, 0.99	0.82	0.27, 1.54	0.68	0.47, 0.97
p for trend	0.01		0.02		0.09	

* Analysis by conditional logistic regression.
† OR, odds ratio; CI, confidence interval.
‡ Among parous women.

were 0.84 (95 percent CI: 0.73, 0.98) for uniparous women, 0.68 (95 percent CI: 0.57, 0.80) for women with three children, and 0.58 (95 percent CI: 0.43, 0.79) for women with five or more births. Among parous women, older age at first birth was associated with a decreased risk of scleroderma (table 2). We examined this relation further by comparing age at first birth using nulliparous women as the referent group. In this analysis, little difference in risk was associated with a first birth before age 20 years (OR = 0.85, 95 percent CI: 0.74, 1.03), but a stronger reduction in risk was found for women with a first birth at age 20 years or older (OR = 0.66, 95 percent CI: 0.59, 0.75).

We repeated the analyses, stratifying by age at hospitalization, to examine whether the observed associations were found among both reproductive-age and postreproductive-age women (table 2). Similar patterns were seen in both groups, but the increased risk associated with nulliparity was stronger for women less than age 45 years at diagnosis (OR = 1.60, 95 percent CI: 1.26, 2.03).

DISCUSSION

The idea that persistent exposure to nonhost cells—microchimerism—could play a role in the development of conditions with autoimmune components such as scleroderma, Sjögren's syndrome, and thyroid disease is receiving increased attention (12). A miniexchange of cells between mother and child takes place throughout pregnancy (13, 14). Fetal cells have been found in the circulatory system of women up to 27 years after pregnancy (15). The mechanism by which these cells eventually are eliminated from the maternal blood is not known. Exposure to nonhost cells, some of which are capable of differentiation into immunocompetent cells, is likely to represent an immunologic event for the mother because these cells express gene products that are inherited from the father and are therefore foreign to the woman.

In the present study, we found an increased risk of scleroderma for nulliparous women compared with parous women. These results corroborate findings in a recent Italian hospital-based case-control study of 46 cases and 153

controls (9). In that study, data were presented by using nulliparous women as the referent group, and the risk of scleroderma was found to be 70 percent lower for parous women (OR = 0.3, 95 percent CI: 0.1, 0.8). Similar to our findings, risk decreased with increasing parity. We observed an increase in risk with younger age at first birth, an association not found in the Italian study.

Women with scleroderma who become pregnant may be at higher risk of some adverse pregnancy outcomes such as premature births and small-for-gestational-age infants (16). Some evidence also exists that prior to disease onset, scleroderma patients have higher rates of infertility and delays in conception. Silman and Black (6) found a tripled rate of fertility problems before diagnosis among women with scleroderma compared with healthy controls. Similarly, Englert et al. (17) reported that both delay in conception and infertility were more common in patients who subsequently developed scleroderma. Thus, it is possible that the associations we observed (higher risk with nulliparity and decreasing risk with increasing parity) reflect subtle immunologic or vascular effects of scleroderma prior to clinical manifestation that reduce the likelihood of conception.

In further exploration of the pregnancy experience, we observed that, for parous women, a younger age at first birth (age <20 years) was associated with increased risk of scleroderma, and the magnitude of the risk was similar to that for nulliparous women. The inverse association with parity was seen most strongly among women whose first birth occurred after age 20 years. The explanation for this observation is not clear.

Strengths of the present study include its size and population-based approach. Exposure (childbearing) was recorded independently of outcome (scleroderma). However, information was not available on pregnancies not resulting in a livebirth. There is little evidence for an association between spontaneous abortion and risk of developing scleroderma (17, 18). In the case-control study by Pisa et al. (9), inclusion of spontaneous and induced abortions had little effect on the observed associations with parity.

Fewer than five controls were available for 12 percent of the cases. However, little difference was found in the age or parity experience of cases for whom there were five compared with fewer than five controls. To explore the potential for possible bias introduced by the difference in number of controls, we repeated our analyses, excluding those for whom there were fewer than five controls; we found that this exclusion had little effect on the results.

Another potential weakness was that this study was restricted to patients hospitalized for scleroderma. However, patients included are likely to be those with the most severe disease manifestations, most likely diffuse scleroderma. Results from a nationwide survey in Iceland indicate that as many as 78 percent of scleroderma patients had been hospitalized at least once (19). Most (91 percent) of the scleroderma patients in the case-control study from Italy had diffuse disease. In the present study, it was not possible to differentiate between patients with diffuse scleroderma and those with limited disease.

Some of the cases identified in the Inpatient Register may have been misclassified; that is, the discharge diagnosis of scleroderma could be incorrect. Unless the alternate, "true" diagnoses were strongly associated with reduced parity, it is most likely that misclassification would have attenuated the observed associations with parity. To assess the accuracy of the discharge diagnosis data, we reviewed the medical records of women discharged for the first time with a primary or secondary diagnosis of scleroderma from the rheumatology and dermatology clinics at the Karolinska Hospital, the largest hospital in the Stockholm region. On the basis of available information in the retrieved records of 129 (out of a total of 133 identified) patients, it was judged that 72 (56 percent) unequivocally fulfilled the 1980 American College of Rheumatology criteria (rheumatology clinic, 63 percent; dermatology clinic, 52 percent). A majority of those not fulfilling the criteria were judged to have localized scleroderma. Some patients had overlap syndromes, such as mixed connective tissue disease.

Another limitation was that date of first disease signs and symptoms was not available in the Inpatient Register. In addition, before 1987, the Inpatient Register did not fully cover all regions of Sweden, so the first scleroderma-related hospitalization of women who were not living in a region covered by the register could have been missed. The median age at first scleroderma-related hospitalization of our cases was about 4 years higher than the median age at diagnosis in a population-based study from Michigan (20). (The proportion of women aged 40–59 years in the 2000 census data from Michigan is similar to that of Sweden (21, 22), so differences in the age distributions of these populations should not have a big effect on the age distribution of scleroderma cases in these areas.) To account for the possibility that some pregnancies could have occurred after debut of insidious scleroderma symptoms or a preliminary diagnosis (but before hospitalization), we repeated the analyses after excluding pregnancies that had occurred within the 2 or within the 5 years before first hospitalization. This restriction had little effect on our results.

Our results do not support the hypothesis that microchimerism—as measured by parity—plays a role in the etiology of scleroderma, corroborating findings of the previous epidemiologic study in this area (9). Microchimerism may be more clearly addressed at the cellular level (e.g., in studies that assess the persistence of nonself cells in circulation or at the site of specific lesions) than in studies relying on more indirect measures of the potential for maternal-fetal cell transfer such as parity. Some aspects of pregnancy, such as preeclampsia or other complications involving the placenta, could affect the maternal-fetal exchange of cells (23) and so may be an appropriate focus of epidemiologic studies.

In conclusion, little evidence exists that childbearing explains the strong female predilection for the disease. On the contrary, it appears that childless women are at increased risk of scleroderma. This finding could reflect subfecundity before clinically evident disease, yet-to-be-identified common causes of infertility and scleroderma, or a protective effect of pregnancy through an unknown mechanism.

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