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The effects of previous Hysterectomy on Lupus

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Summary

Hysterectomy is one of the most common surgical procedures performed in United States, and currently, one in three women in United States has had a hysterectomy by the age of 60 years. Systemic lupus erythematosus (SLE) is a common autoimmune disease and especially targets women of childbearing age at least 10 times higher than men, which reflects the major role of female sex hormones. In this retrospective study, we evaluate the potential effects of previous hysterectomy in our lupus cohort. Data collected from study subject questionnaires were obtained from the Lupus Family Registry and Repository (LFRR) at the Oklahoma Medical Research Foundation. Hysterectomy data were available from 3389 subjects. SLE patients with a positive history of hysterectomy have been selected and compared with matched lupus patients with a negative history of hysterectomy and healthy controls. Association analyses were performed, and the P values and adjusted odds ratios (ORs) were calculated. SLE patients with a negative history of hysterectomy more likely had kidney nephritis or positive anti-dsDNA than age-matched SLE patients with a history of hysterectomy before disease onset. This effect was independent of ethnicity with an OR of 6.66 (95% CI = 3.09–14.38, $P = 1.00 \times 10^{-8}$) in European patients and 2.74 (95% CI = 1.43–5.25, $P = 0.001$) in African-Americans. SLE patients with a positive history of hysterectomy before disease onset also had a later age of disease onset ($P = 0.0001$) after adjustment for age and race. Our findings support the notion that the influence of female sex hormones in SLE and various clinical findings are tremendous and that surgical menopause such as this could significantly affect the outcome of disease and clinical manifestations

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, characterized by autoantibody production and deregulation of T and B cells. SLE has a prevalence rate of ~40 per 100,000 individuals and primarily affects women of childbearing age (F:M ratio 9:1) (1). Minority groups especially African-Americans are three times more likely to be affected than European-Americans with a clinically more severe phenotype than other racial groups (2–4). After Cesarean section, hysterectomy is the second most common surgery among women in the United States. One in three women in the United States has had a hysterectomy by age 60. There are many reasons for hysterectomy from benign fibroid or malignant tumors or endometriosis, to persistent bleeding or chronic pelvic pain. According to the National Center

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for Health Statistics (NCHS), of the 617,000 hysterectomies performed in 2004, 73% also involved the surgical removal of the ovaries (5). This procedure therefore could profoundly affect the female sex hormone balance and subsequently the incidence or severity of complex diseases such as lupus that have a female predominance. In this retrospective study we sought to examine this potential effect based on the self-reported questionnaire inquiry in our patients with SLE.

Materials and methods

Data were obtained from the Lupus Family Registry and Repository (LFRR) at the Oklahoma Medical Research Foundation. Each affected and healthy control was asked to complete a questionnaire that requested extensive information from the subject. In addition, SLE affected participants were also asked to complete a supplemental questionnaire with detailed information about their disease history. The medical record was also obtained for each affected and was reviewed by a nurse, physician's assistant, or physician and the relevant information was extracted (6). All subjects classified as having SLE met the 1982 revised ACR criteria as amended (7). The Institutional Review Board of Oklahoma Medical Research Foundation, approved the study. Ethnicity was self-reported and verified by parental and grandparental ethnicity, when known. As part of the questionnaire, female subjects were asked whether they had a history of hysterectomy and at what age. Association analyses and Student's *t* tests were performed and the *p* values, odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated. For analyses with the ACR criteria, Bonferroni corrections for multiple comparisons were not conducted since the ACR criteria are not completely independent.

Results

Data for hysterectomy were available in 3389 European or African-American subjects including 1006 females with SLE, 490 female healthy controls and 1893 family members. From 1006 cases with SLE, only independent (that is unrelated) cases have been used for study (885).

We initially compared the frequency of hysterectomy between independent lupus patients and healthy controls. Table 1 shows the demographic characteristics of this population. Because history of hysterectomy was not present before 20 years of age in either SLE cases or controls, we excluded subjects younger than 20 years old. We observed a significantly increased rate of this procedure in SLE patients compared to controls in both European-Americans and African-Americans (Table 1). In European-Americans 52% of lupus patients had a positive history of hysterectomy compared to 25% of healthy controls (OR=3.25, 95% CI=2.41–4.38, $P<10^{-6}$). Similarly, in African-American 36% of SLE patients has a hysterectomy compared to 19% of healthy controls (OR=2.42, 95% CI=1.48–3.95, $P=0.0003$) (Table 1). Among SLE subjects, there was no significant difference in the rate of hysterectomy before or after SLE onset and therefore this trend remained significant when only patients with history of hysterectomy before SLE onset were compared to matched controls (in European-Americans (OR=2.17, 95% CI=1.50–3.05, $P<10^{-5}$), in African-Americans (OR=1.86, 95% CI=1.09–3.19, $P=0.02$). In addition, regardless of ethnicity, lupus patients tended to be younger than healthy controls when this surgery was performed with a mean age of 35.2 (95% CI=34.28–36.19) in SLE patients compared to 38.6 (95% CI=36.93–40.26) in controls ($P=0.0006$). The distribution of parity and number of previous pregnancies between cases and controls were similar and the median number of children in both cases and controls were 2. We used other surgeries as a control. When cases and controls were compared for cholecystectomy before SLE onset or tonsillectomy there was no significant difference between groups (8% vs 11% and 42% vs 41% respectively). Increase rates of hysterectomy also were observed among family members of SLE patients. In European-Americans, 55% of unaffected family members with age above 20,

had positive history for hysterectomy. In African-Americans, 47% of family members were positive (Table 1). The highest rate of hysterectomy was observed in group of independent individuals who claimed that they had lupus but they didn't meet the minimum 4 out of 11 ACR criteria necessary for diagnosis of SLE. In this group, 62% of European-Americans and 56% of African-American had history of previous hysterectomy (Table 1) and in compare to controls odds ratios of (OR=4.80, 95% CI=3.24–7.08) and (OR=5.38, 95% CI= 2.96–9.80) were observed, respectively (Table 1).

Next, two independent groups of lupus patients were selected for comparison, those with positive (267 European-Americans, and 136 African-Americans) and negative history of hysterectomy (241 European-Americans and 241 African-Americans) (Table 1). Generally, the mean age of SLE onset in patients with a history of hysterectomy was significantly higher than that of patients with negative history ($P=0.0001$) regardless of race. Therefore, to determine the possible effect of hysterectomy on SLE disease onset, SLE patients who had a hysterectomy prior to SLE onset were matched by age-decade with lupus patients with no history of hysterectomy. The age window of 30 to 60 years old in the 3 decade strata (30–39, 40–49, 50–59) were included to match the age at study between two groups (Table 2). Indeed, in each decade window of age, SLE patients with hysterectomy performed before SLE onset, had significantly higher age of SLE onset than SLE patients with a negative history of hysterectomy (Table 2). In addition, in the group of SLE patients with history of hysterectomy prior to SLE onset, in general, there was a clear gap of more than 10 years between the mean age of hysterectomy 32.9, (95% CI=31.82–33.89) and the mean age of SLE onset (44.4, 95% CI =43.37–45.49), disregard of ethnicity $P=0.0001$.

We then evaluated the ACR criteria frequencies and auto-antibody titers between the two groups. Since an early age of onset is associated with more severe disease, SLE patients who had a hysterectomy prior to SLE diagnosis were selected and matched by the age of SLE diagnosis, race and age of participation in the study to the independent group of SLE patients with negative history of hysterectomy (Table 3). SLE patients with a negative history of hysterectomy had significantly higher incidence of nephritis (OR=6.66 in European-Americans and 2.74 in African-Americans) than age-matched SLE patients who had a hysterectomy before SLE onset (Table 3). Similarly, anti-dsDNA and anti-SM were more frequent in the group of patients with a negative history for hysterectomy while there was no significant difference in anti-Ro antibodies (Table 3). Other ACR criteria were suggestive or not significant (data not shown). Furthermore, in the group of independent patients that had a hysterectomy after SLE diagnosis, 91% expressed nephritis before the hysterectomy procedures.

Finally, by reviewing the available medical records, from cases with history of hysterectomy before SLE, 81 European-Americans and 27 African-American cases have been identified with concomitant unilateral or bilateral oophorectomy. None of 81 European cases had evidence of kidney nephritis (OR=infinity) and in African-American, 2 cases were identified (OR=13.2, 95% CI=3.02–58.02). Similar trend were observed in other ACR criteria in this particular subgroup.

Discussion

In this retrospective case control study we investigated the possible effect of hysterectomy on SLE disease onset and ACR criteria in our available lupus patients. We found that lupus patients with a history of hysterectomy before SLE onset, had milder disease with less nephritis, less anti-dsDNA and a later age of disease onset than did lupus patients with a negative history for this procedure. This effect was observed in both European-American and African-American subjects. Biologically, the protective effect of hysterectomy with oophorectomy which causes

a surgical menopause, can be expected. To our knowledge, however, there are no recent reports that address this issue in SLE. In a study reported in 1985, Grimes et al. suggest the possible protective effect of prior hysterectomy or tubal sterilization on SLE because their SLE cases were less likely to have a hysterectomy than controls (OR= 0.54, 95% CI=0.29–0.99) (8). However their sample sizes were small. Thus, once adjusted for age, the finding was not statistically significant 0.73 (95% CI= 0.40–1.50) and simultaneous adjustment for age and race was not performed. In our study, SLE patients were, indeed, more likely to have had hysterectomy both before and after SLE onset than age matched controls (Table 1). When comparing cholecystectomy or tonsillectomy before SLE onset, there were no significant differences between cases and controls.

In our data, the increased rate of hysterectomy also was observed among family members of lupus patients compared to normal controls and, interestingly, the highest trend was observed among subjects with intermediate lupus (i.e. those subjects that failed to meet the 4 criteria for SLE diagnosis) (Table 1). This further suggests that a hysterectomy may help to protect against full blown disease manifestations. Indeed in this group of intermediate lupus subjects with borderline criteria, those with past surgical history of hysterectomy, had either a negative ANA or low titer (≤ 120) at the time of participation in the study compared to those with a negative history (European-American 73% vs. 50%, OR=2.72, 95% CI=1.43–5.18, $P=0.002$); African-Americans 67% vs. 47% OR=2.36, 95% CI=1.03–5.38, $P=0.03$). Similar trends were observed among controls and other family members but the results were only suggestive (data not shown).

To our knowledge there is no report in humans to examine any possible effect of previous hysterectomy on ACR criteria or age of disease onset in lupus. Our data suggest that some ACR criteria, especially those related with more severe disease such as nephritis and the presence of anti-dsDNA antibodies, could be more influenced by previous hysterectomy than other criteria.

It has been known for decades that the strongest risk factor for SLE is female gender. It has been shown that the sex ratio at age of onset rises with puberty from 2:1 to almost 10:1 in young adulthood and declines with female menopause in the sixth decades (9). Studies performed in (NZBxNZW) F1 hybrid mouse, a murine model of SLE, also support the role of female hormones in the modulation of the autoantibody titer and development of renal disease and death (10). However, the relationships between the reproductive factors and sex hormones are complex and it is difficult to explain the pathogenesis of SLE by hormone factors. Other effects, such as X chromosome gene dose effect or susceptibility genes acting in one sex or the other also contributed (11,12).

It is important to mention that hysterectomy by itself could affect the ovarian function and could result in early menopause and premature ovarian failure in some cases (13). Therefore, even hysterectomy without ovariectomy may be potentially important in SLE. Although the rate of concomitant ovariectomies that more importantly affect the female hormone balance were not available in all of our cases, however in limited available data in medical records, from 155 cases with history of hysterectomy before SLE onset, 81 European cases have been identified with concomitant history of unilateral or bilateral oophorectomy and strikingly none of them had any evidence of kidney nephritis. Similar trend were observed in African-American cases as described previously however the number of cases were limited and further studies are needed to confirm these preliminary findings. Furthermore, endometrial and ovarian autoantibodies have also been reported to be commonly seen in female SLE patients than healthy controls, although significance of these autoantibodies are not clear (14).

Based on separate query from the general questionnaire on whether or not the subjects take hormones, more than 90% of our patients who had undergone hysterectomy were on hormone replacement therapies (HRT) at the time of participation to the study. However this query didn't address the dosage, duration of therapy or combination of hormones used. Usually patients who have undergone a hysterectomy are given estrogen therapy alone while a progestin is added to estrogen in postmenopausal women with a uterus, in order to prevent endometrial hyperplasia or cancer (15). The decision for using long-term HRT depends on many factors such as age, health status and cardiovascular disease risk factors. On average, only 20% of HRT users are maintained treatment for at least 5 years or more (15). In our data, conditional analyses based on hormone therapy, didn't affect the results in ACR criteria and in group of patients with negative history for hysterectomy there was no significant difference in ACR criteria based on this query.

Based on our available medical records we could not find any significant difference of the underlying causes of hysterectomy between cases and controls and uterine fibroids or uterine bleeding were common in both groups as expected. Without a doubt underlying female hormonal balance plays a key role in leading to conditions such as persistent uterine bleeding or fibroids that ultimately need surgical treatment. This balance is under control of genetic factors as well as environmental elements such as diet and xenoestrogen consumptions, or a combination of both. We speculate that SLE patients may be more likely to have irregularities in hormonal balances (e.g a dominant estrogen state) and are, therefore, more likely to have a hysterectomy due to the complications of these irregularities. These patients would sooner reach early menopausal states with less severe disease manifestations. The similar observed trend in SLE family members can be explained by shared genetic and environmental elements. Further studies are needed to confirm or refute this possibility.

Currently, our understanding of the link between environmental risk factors and rheumatic diseases such as SLE is very limited. In conjunction with whole-genome scans that have changed dramatically our understanding of complex diseases such as SLE, the whole-environmental scans could change dramatically the capacity to define gene-environmental risk factors in the future. This can only be possible by integrating an extensive exposure questionnaire into a genetics database.

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Table1

Distribution of independent cases and controls by history of hysterectomy.

	History of hysterectomy*		Odds Ratio (95% CI)	P value
	Yes	No		
European-American				
Cases	267	241	3.25 (2.41–4.38)	p<1.00E-06
Controls	88	258		
Family members [†]	431	356	3.54 (2.68–4.69)	p<1.00E-06
intermediate ^{††}	108	66	4.80 (3.24–7.08)	p<1.00E-06
African-American				
Cases	136	241	2.42 (1.48–3.95)	3.00E-04
Controls	24	103		
Family members	171	187	3.92 (2.40–6.40)	p<1.00E-06
intermediate	54	43	5.38 (2.96–9.80)	p<1.00E-06

* Excludes women <20 years of age.

[†] One healthy family member from each pedigree from LFRR collection

^{††} intermediate: subjects that failed to meet the 4 criteria for SLE diagnosis

Table 2

Comparison of mean age of SLE onset between group of SLE patients with hysterectomy performed before SLE onset and those cases with negative history of hysterectomy matched based on age of participant in three separate decades (30–39, 40–49, 50–59) for each ethnicity.

Age at study (yr) *	Mean age of SLE onset (yr)		P values
	Hysterectomy performed before SLE onset N=128 [†]	SLE patients with negative history of Hysterectomy N=191 [†]	
European-American			
Age 30–39	33.2 (27.89 – 38.44)	23.9 (22.18 – 25.52)	1.00E-03
Age 40–49	38.8 (36.64 – 41.03)	31.4 (29.60 – 33.17)	1.00E-04
Age 50–59	46.1 (44.12 – 48.09)	38.6 (36.11 – 41.02)	1.00E-04
African-American			
Age 30–39	29.2 (23.60–34.90)	24.8 (23.45– 26.18)	1.20E-01
Age 40–49	37.2 (34.14 –40.26)	31.4 (29.61–33.17)	1.00E-03
Age 50–59	46.8 (42.75– 50.85)	37.2 (34.33 – 40.13)	3.00E-04

* Age of subjects at the time of participation into the study.

[†] Number of independent cases in the age window of 30 and 60 years old for each ethnicity.

Table 3

Demographic characteristics of age-matched female SLE patients under study and ACR criteria. In each race, (European and African-American), SLE cases with hysterectomy performed before diagnosis of lupus compared to SLE cases without history of hysterectomy and match with age and the age of SLE onset.

European-American	SLE cases without Hysterectomy N=134	SLE cases with Hysterectomy* N=155	OR (95% CI)	P values
Mean age of participants	46.3 (44.76–47.8) [†]			
Mean age of SLE onset	37.5 (36.03–38.95) [†]			
Nephritis	39	9	6.66 (3.09–14.38)	1.00E-08
immunologic	97	69	3.27 (1.99–5.35)	1.00E-06
Anti-dsDNA	33	13	3.57 (1.78–7.12)	1.00E-04
Anti-SM	17	6	3.61 (1.38–9.45)	3.00E-03
Anti-Ro	33	26		NS
African-American	SLE cases without Hysterectomy N=140	SLE cases with Hysterectomy* N=61		
Mean age of participants	41.3 (39.79–42.82) [†]			
Mean age of SLE onset	36.2 (34.87–37.59) [†]			
Nephritis	72	17	2.74 (1.43–5.25)	1.00E-03
Anti-dsDNA	57	9	3.96 (1.81–8.68)	3.00E-04
Anti-Sm	52	13	2.18 (1.08–4.40)	2.00E-02
Anti-Ro	36	17		NS

* SLE cases with hysterectomy prior to SLE onset

[†] The two selected groups in each ethnicity were matched by age and age of SLE onset.