

Excess Female Siblings and Male Fetal Loss in Families with Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* Systemic lupus erythematosus (SLE) occurs more frequently among women than men. We aimed to determine whether the male-female ratio in SLE families is different from what would be expected by chance, and whether excess male fetal loss is found.

Methods. All patients with SLE met the revised American College of Rheumatology classification criteria, while unaffected subjects were shown not to satisfy these same criteria. Putative family relationships were confirmed by genetic testing. Pregnancy history was obtained from all subjects, including unrelated control women. Adjusted Wald binomial confidence intervals were calculated for ratio of boys to girls in families and compared to the expected ratio of 1.06.

Results. There were 2579 subjects with SLE, with 6056 siblings. Considering all subjects, we found 3201 boys and 5434 girls (ratio 0.59, of 95% CI 0.576–0.602). Considering only the SLE-unaffected siblings, there were 2919 boys and 3137 girls (ratio 0.93, 95% CI 0.92–0.94). In both cases, the ratio of males to females was statistically different from the known birth rate. Among patients with SLE as well as among their sisters and mothers, there was an excess of male fetal loss compared to the controls.

Conclusion. Siblings of patients with SLE are more likely than expected to be girls. This finding may be in part explained by excess male fetal loss, which is found among patients with SLE and their first-degree relatives. (First Release Feb 1 2013; J Rheumatol 2013;40:430–4; doi:10.3899/jrheum.120643)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS SEX RATIO FETAL LOSS PREGNANCY

Systemic lupus erythematosus (SLE) is a chronic, inflammatory disease that can involve virtually any organ system. The disease is complex in its clinical manifestations and serology as well as genetics^{1,2,3}. However, patients have in common the finding of autoantibodies that typically bind nuclear components². SLE is more common and more severe in Americans with sub-Saharan African ancestry compared to white Americans⁴.

Women are affected with SLE about 10 times more frequently than are men, notwithstanding that men have more severe disease⁵. The female predominance for the incidence of SLE holds for all age groups, although it is less extreme for prepubertal children and women beyond menopause⁶. There are abnormalities in sex hormones among women and men with SLE but when determined at the onset of illness prior to therapy, 1 study has found no differences in estrogen or androgen serum levels⁷. Another cross-sectional study of men with SLE found no difference in androgen levels compared to men with other chronic illnesses without a sex bias⁸.

There are several theories for the female bias found in SLE other than sex hormone differences. We have proposed that risk is related to the number of X chromosomes, not sex. This hypothesis is based on an increased risk of SLE in men with 47,XXY (Klinefelter's syndrome) and a lower risk of SLE among women with 45,XO (Turner's syndrome)^{9,10} as well as an increase of 47,XXX among women with SLE (unpublished data). In a study of pediatric patients with SLE and their families, Moorthy and colleagues found fewer male siblings than expected, and proposed a genetic susceptibility factor that gives boys a risk of fetal demise and girls a risk of SLE¹¹. These 2 ideas are not mutually exclusive. The parsimonious explanation is a gene on X that both is overexpressed in individuals with 2 X chromosomes compared to 1, and imparts a risk of SLE to girls as well as a risk of fetal death to boys.

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We undertook our study to determine whether there are excess female siblings in families with SLE (both adult-onset and pediatric-onset). In addition, we sought to determine whether male fetuses are found in excess among spontaneous abortions and stillbirths in families with SLE.

MATERIALS AND METHODS

Lupus Family Registry and Repository (LFRR). We have been collecting and storing clinical data, sera, plasma, DNA, peripheral blood mononuclear cells, and family structure data for almost 20 years from families with SLE^{12,13}. Putative SLE patients complete an extensive questionnaire and are interviewed by trained personnel, and their medical records are reviewed to ensure that the revised American College of Rheumatology SLE classification criteria are met^{14,15}. SLE-unaaffected family members complete the questionnaire and are interviewed if there is any indication that undiagnosed SLE might be present. All subjects have antinuclear antibody, anti-dsDNA, antiphospholipid, and anti-extractable nuclear antigen determined in the Oklahoma Medical Research Foundation Clinical Immunology Laboratory.

Family structure. Complete family structures are obtained for all patients and families. Relationships have been shown to be consistent with the represented relationships through genetic testing, originally with micro-satellite markers and now with single-nucleotide polymorphism typing.

Pregnancy history. History of pregnancy and its complications were recorded for all patients with SLE as well as their female relatives. These data included total number of pregnancies, number of live-born infants, spontaneous abortions, induced abortions, and stillbirths (defined as delivery of a nonviable infant beyond the first trimester of pregnancy). In addition, subjects were asked the sex of the conceptus for all pregnancies, including those that were not completed to term delivery.

Statistics. We compared categorical data using the chi-square test. P values < 0.05 were considered significant. Adjusted Wald binomial confidence intervals were calculated for ratio of boys to girls in families and compared to the expected ratio of 1.06, that is, 13 male births for every 12 female births¹⁶.

RESULTS

We studied 2578 subjects with SLE, who in total had 6056 siblings. Considering all individuals, there were 3201 boys and 5434 girls in the sibships of patients with SLE (Table 1). Thus, the ratio of boys to girls was 0.59 (95% CI 0.576–0.602). The CI do not include the expected ratio of 1.06 boys to girls. Thus, there were significantly fewer boys in these SLE families than expected.

There is a possible statistical explanation. The boys-to-girls ratio in sibships of patients with SLE may be skewed because of the SLE, which is 90% female. That is, because inclusion of the SLE probands biases the data, these individ-

Table 1. The sibships of patients with systemic lupus erythematosus (SLE) have excess girls compared to boys with inclusion of all siblings, whether the SLE patient is included or excluded. The 95% CI did not cross the expected ratio of 1.06 in either case.

	All Siblings	SLE Patients Excluded
Boys, n	3201	2919
Girls, n	5434	3137
Ratio	0.59 (95% CI 0.576–0.602)	0.93 (95% CI 0.921–0.938)

uals should be omitted from the analysis. Thus, to correct for this potential bias, we excluded all subjects with SLE and examined the sibling sex ratio. In this case, there were 6056 non-SLE-affected siblings of whom 2919 were boys and 3137 were girls (Table 1). Again, the ratio of 0.93 was less than expected and the 95% CI of 0.921 to 0.938 did not include the expected ratio of 1.06.

In addition to the Moorthy, *et al* study of pediatric SLE¹¹, another study also found a skewing of the sex ratio among the siblings of patients with SLE¹⁷. That study noted that the sex ratio was only biased toward girls in the pregnancy that produced the patient with SLE and the subsequent pregnancy. We addressed this issue by examining the sex ratio in the pregnancy just before and just after the pregnancy that produced a child destined to develop SLE. This was performed in a random sample of 85 families from the LFRR in which all needed information was available, such as birth order, sex, and participation of all siblings. We found among children born immediately before the child who developed SLE that there were 11 boys and 29 girls (0.39 ratio). In the pregnancy just after the one that produced a child who eventually had SLE, there were 19 boys and 34 girls (0.56 ratio). The sex ratio distortion before and after the SLE pregnancy, respectively, differed from the expected ($OR_{BEFORE} = 2.4$, chi-square = 6.73, $p < 0.01$, and $OR_{AFTER} = 1.93$, chi-square = 5.54, $p < 0.05$). So the sex bias was greater in the pregnancies prior to the birth of the child who would go on to acquire SLE, which stands in contrast to the previous report, in which the sex bias for girls was found just after the “SLE” pregnancy. Meanwhile, the difference we found between the pregnancy just before and just after the SLE birth was not statistically significant (chi-square = 0.72, $p = 0.52$).

We also studied the sex distribution of fetal loss. Among the patients with SLE, there were 48 spontaneous abortions or stillbirths in which the sex was known. Of these, 15 were female and 31 were male infants (ratio = 0.326, 95% CI 0.208–0.4710). In addition, among the mothers and sisters of patients with SLE, we found 95 pregnancy losses in which the sex of the fetus was known. There were 31 female and 64 male fetuses among these (ratio 0.484, 95% CI 0.366–0.604). Among 1500 female controls, who were matched for age, sex, and ethnicity to the patients with SLE, the ratio of male-to-female fetal loss was 0.95.

DISCUSSION

SLE is found among women about 10 times more often than among men. In fact, a female predominance is present for almost all diseases now considered autoimmune¹⁸. Despite clear and known effects of sex hormones on the immune system, an explanation of autoimmune disease sexual dimorphism on the basis of sex hormones has not been elucidated¹⁹, although some new theories have been reported²⁰. There may not be a common mechanism across

all autoimmune diseases. Autoimmune thyroid disease²¹ and type 1 diabetes mellitus²² are associated with Turner's syndrome (female 45,XO), but this sex chromosome aneuploidy is probably not associated with SLE^{9,10}.

In a very large cohort of patients with SLE, we found that there were fewer boys than expected among the siblings of the patients. The ratio of boys to girls, both considering the subjects with SLE or excluding them, is very similar to that found in a small cohort of patients with pediatric-onset SLE¹¹. In their study of 91 pediatric patients with SLE, Moorthy and colleagues¹¹ found a boy-to-girl ratio of about 0.6 with SLE patients included and a ratio of 0.92 without SLE patients. We found ratios of 0.59 and 0.93, with and without SLE patients, respectively. Of interest, Moorthy and colleagues did not find an abnormal male-to-female ratio among the siblings of patients with systemic onset juvenile idiopathic arthritis, a disease that does not have a sex bias¹¹. Only about 10% of our patients have pediatric-onset SLE. The effect we found when excluding the SLE probands is the statistically correct one, and is present in families with either adult or pediatric disease onset (data not shown).

Another study also found that the families of patients with SLE have more girls than expected. Oleinick studied 191 patients with SLE and their families¹⁷. There were 279 male siblings and 302 female siblings, giving a ratio of 0.923. This value is strikingly similar to what we found, as well as that found among pediatric-onset SLE¹⁰. However, the strongest bias in sex of siblings of patients with SLE was found in the pregnancy just after the birth of the patient with SLE, with no sex bias found in the pregnancy preceding the SLE pregnancy. The author concluded that there was an environmental factor leading to male fetal demise and female SLE because the sex bias was not uniform across the siblings. However, among a much larger number of patients with SLE and their families (2578 subjects with SLE and 6056 siblings), we found that the sex bias occurs both before and after the birth of the sibling who went on to have SLE.

Neither of the previous studies of sex bias among the families of patients with SLE had studied the sex of infants spontaneously aborted or stillborn. Many women in our cohort did not know the sex of fetuses aborted in the first trimester, so our data come from a proportion of pregnancies that were not carried to term. There is no reason to suspect that the women in these SLE families are more likely to know the sex of aborted or stillborn males, however. In any case, we found that aborted or stillborn fetuses were twice as likely to be male. This was true for patients with SLE as well as their sisters and mothers.

Previous data of a sex bias just proximal to the birth of the SLE-affected subject were interpreted to mean an environmental factor was present¹⁷. Two pieces of data address this question. First, we found increased male fetal loss not only among patients with SLE but also among their first-degree relatives, mothers and sisters who were not

likely to share a common environment while pregnant. Second, we did not find that the sex bias among SLE siblings is confined to the pregnancy just after the SLE pregnancy. Thus, our data do not indicate an environmental component occurring around the birth of the patient with SLE.

Our current data, along with our previous data that the number of X chromosomes is a risk factor for SLE, can be combined into a single genetic possibility. About 20% of genes on the X chromosome are not inactivated by typical lyonization, which is mediated by CpG methylation²³. Thus, one possibility is that there is a non-inactivated X chromosome gene that has increased expression depending upon the number of X chromosomes. Or an X chromosome gene could present a risk of fetal demise when homozygous, as in 46,XY males. But when heterozygous, as in most 46,XX females and 46,XXY males, the gene imparts an increased risk of SLE. Indeed there is an example of such a gene acting in this way in another disease. Incontinentia pigmenti, a skin pigmentation disorder with other associated abnormalities²⁴, is caused by mutation in the NEMO gene (also known as IP2), which is located at Xq28²⁵. The gene product is I κ B β , one of the 2 subunits of the IKK kinase that mediates the nuclear factor- κ B signaling cascade²⁶. Inheritance of this gene by a male conceptus most commonly results in fetal death, while the disease is found only in those with 2 X chromosomes.

There are other possibilities. Wallace has proposed that a gene on the Y chromosome might increase risk of fetal demise in males and therefore lead to the sex bias of SLE²⁷. This does not explain an increased risk of SLE in 47,XXY men⁹, or in 47,XXX women compared to 46,XX women (Scofield and Harley, unpublished data). A gene on an autosomal chromosome could be expressed in the male fetuses only and predispose to spontaneous abortion or stillbirth, and then in postnatal life be expressed to predispose to SLE. There are a number of factors that change the sex ratio of live births. These include but are not limited to pre-eclampsia, maternal fatty liver, maternal measles, maternal chronic hepatitis B, maternal glucose, maternal multiple sclerosis, maternal age, polycystic ovarian disease, breast cancer, paternal (both parents) hormone levels at the time of conception, race/ethnicity, and even frequency of coitus²⁸. For most of these factors, we do not have any information in our cohort, but hepatitis B may account for much of the sex ratio differences in the world²⁹.

Autoantibodies are another intriguing possibility. The HY antigens are encoded on the Y chromosome, and therefore are present only in male cells. Women develop these antibodies after an allogeneic bone marrow transplant in which the donor was male; and some women develop antibodies against these antigens after pregnancy with a boy^{29,30}. The presence of anti-HY antibodies is associated with secondary pregnancy loss (that is, after a viable birth),

with spontaneous abortions of male fetuses, and an increased ratio of female-to-male live births³¹. Antibodies against NMDA are also of interest. These antibodies occur spontaneously or as a paraneoplastic process, especially associated with teratoma. In addition, these antibodies are related to SLE. Immunization with a peptide mimotope of DNA results in not only anti-DNA but also anti-NMDA. Pertinent to our results, recent data demonstrate that female mice immunized in this way have more male offspring than expected because of the demise of female fetuses³². The effect on female fetuses is mediated by a sexually dimorphic expression of NMDA in the brain. These findings, while opposite in terms of the affected sex, show in principle that maternal antibodies may cross the placenta and affect the fetus in a sex-specific manner³². Thus, autoantibodies can induce sexually specific lethal damage to the developing fetus. In human disease, 2 pregnancies complicated by anti-NMDA encephalitis have been reported, with delivery of normal infants. However, the sex of the infants was not given³³.

It is easy to suppose that patients with SLE might be more likely than non-SLE-affected women to produce such antibodies. Further, the relatives of patients with SLE are more likely to have autoantibodies than controls without a family history of SLE^{34,35,36}. Production of autoantibodies, although not likely directly pathogenic, is associated with recurrent fetal loss in the first trimester of pregnancy^{37,38,39,40}. Thus, it is possible that anti-HY antibodies in patients with SLE and their relatives are responsible for the lower number of male siblings and the increased loss of male fetuses. Conversely, antiphospholipid antibodies are commonly found in patients with SLE and are associated with late-term pregnancy loss, but this loss does not show a sex bias⁴¹.

Women with SLE definitely have lower rates of birth compared to healthy controls^{42,43}. A lower rate of male births may in part explain this difference. This effect could be genetic or environmental, such as that due to autoantibodies. It remains to be determined which of the possible mechanisms are involved in the lower ratio of male to female siblings in families with SLE and the increase in male fetal loss. Elucidating mechanisms that are responsible for these findings may greatly advance knowledge of the X chromosome dose effect in SLE, the sex bias in SLE families, and why women, and occasionally some men, acquire SLE.

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