

Title: Risk of Allergic Conditions in Children Born to Women with Systemic Lupus Erythematosus

Authors: Julie Couture¹, MD; Moshe Ben-Shoshan², MD; Christian A. Pineau³, MD; Susan Scott⁴, MSc; Ann E. Clarke⁵, MD, MSc; Sasha Bernatsky^{3,4}, MD, PhD; Evelyne Vinet^{3,4}, MD, PhD

Authors' Affiliation:

¹Department of Pediatrics, Division of Rheumatology, McGill University Health Centre, Montreal, Canada, H4A 3J1;

²Department of Pediatrics, Division of Allergy and Clinical Immunology, McGill University Health Centre, Montreal, Canada, H4A 3J1;

³Division of Rheumatology, McGill University Health Centre, Montreal, Canada, H3G 1A4;

⁴Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Canada, H3A 1A1;

⁵Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Canada, T2N 1N4

Address for Reprints and Corresponding Author:

Julie Couture, MD

Montreal Children's Hospital, McGill University Health Center, 1001 Décarie Blvd., Room A04.6304, Montreal (PQ), Canada, H4A 3J1

Phone: (514) 412-4400 ext. 22621; Fax: (514) 412-4365; julie.couture2@mail.mcgill.ca

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ABSTRACT

Objective: Limited evidence suggests a potentially increased risk of allergic conditions in offspring born to women with systemic lupus erythematosus (SLE). In a large population-based study, we aimed to determine if children born to SLE mothers have an increased risk of allergic conditions compared to children born to mothers without SLE.

Methods: Using the "Offspring of SLE mothers Registry (OSLER)", we identified children born live to SLE mothers and their matched controls, and ascertained allergic conditions (including asthma, allergic rhinitis, eczema, urticaria, angioedema, and anaphylaxis) based on ≥ 1 hospitalization or ≥ 1 or 2 physician(s) visit(s) with a relevant diagnostic code. We adjusted for maternal age, education, race/ethnicity, obstetrical complications, calendar year of birth, sex of the child, and maternal medication.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean follow-up was 9.1 (SD 5.8) years. As opposed to controls, more children born to mothers with SLE had evidence of allergic conditions [43.9% (95% CI 40.4, 47.6) versus 38.1% (95% CI 37.0, 39.1)]. In multivariate analysis (n=9212), children born to SLE mothers had an increased risk of allergic conditions versus control children (OR 1.35, 95% CI 1.13, 1.61).

Conclusion: Compared to children from the general population, children born to women with SLE may have an increased risk of allergic conditions. Genetics, shared environmental exposures, as well as in utero exposure to maternal autoantibodies and cytokines may mediate this increased risk.

SIGNIFICANCE AND INNOVATIONS

- ☐ The risk of allergic conditions in children born to women with SLE has only been evaluated, to date, in a handful of small observational studies.
- ☐ Genetics, shared environmental exposures, as well as in utero exposure to maternal autoantibodies and cytokines might explain the increased risk of allergic conditions in these children.

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) have a dysregulated immune system, and may have an increased susceptibility to develop allergic conditions. Immunological correlations between SLE and allergic diseases have been suggested.[1] Recent observations propose that not only T-helper type 1 (Th1) cells but T-helper type 2 (Th2) cells can contribute to SLE, postulating that autoreactive IgE and the activation of basophils may promote the production of autoantibodies in SLE.[2]

Some observational studies suggest an increased prevalence of allergic conditions in SLE patients compared to unaffected subjects,[3,4,5] while other studies have failed to do so. Discrepancies between cases and controls, particularly regarding age, race/ethnicity and sex, might explain the divergent conclusions of these previous studies.

Regarding the offspring of SLE patients, one could argue that as women with SLE have more obstetrical complications than unaffected women, children born to mothers with SLE might have an increased risk of allergic conditions compared to children from the general population. Indeed, there is some evidence that obstetrical complications increase the risk of allergic conditions. For instance, preterm birth and lower birth weight have been associated with an increased risk of developing childhood asthma.[6] Furthermore, even if in one study no difference in autoantibody levels (antinuclear antibodies (ANA), antibodies to extractable nuclear antigens (ENA), and anti-double stranded DNA (anti-dsDNA) antibodies) has been found between allergic and non-allergic SLE patients[3], it is unclear if transplacental passage of maternal autoantibodies may predispose children born to mothers with SLE to develop allergic conditions. Only a handful of small observational studies have evaluated the risk of allergic

conditions in offspring born to women with SLE, showing a potentially increased likelihood.[7,8,9] These studies had a small sample size (between 36 and 153 children), did not systematically include an unexposed group and did not specifically assess allergic conditions.

Based on these available data, we aimed to determine, in a large population-based study, if children born to SLE mothers have an increased risk of allergic conditions compared to children born to mothers without SLE.

METHODS

Study Cohort

We used the Offspring of SLE mother Registry (OSLER), a population-based cohort of 719 children born to mothers with SLE, matched to 8493 control children in the province of Quebec, Canada. All women with SLE who had at least one hospitalization for a delivery (stillbirth or live birth), between January 1989 and December 2009, were identified using data from “Maintenance et exploitation des données pour l’étude de la clientèle hospitalière (MED-ECHO)” and “Régie de l’assurance maladie du Québec (RAMQ)” billing database. MED-ECHO is the administrative database collecting information on all hospitalizations in Quebec since 1987. The RAMQ billing database records all publicly reimbursed physician encounters in Quebec.

Exposure of Interest

Women were identified as SLE cases (based on a validated definition,[10] using International Classification of Diseases (ICD)-9 code 710.0 or ICD-10 code M32) if they had any of the following: 1) ≥ 1 hospitalization with a diagnosis of SLE (either primary or non-primary) prior to the delivery, 2) a diagnosis of SLE (either primary or non-primary) recorded at the time of their hospitalization for delivery, or 3) ≥ 2 physician visits with a diagnosis of SLE, occurring 2

months to 2 years apart, prior to the delivery. These SLE women were individually matched at least 4:1 to women for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery.

Mother-child linkage was done using the encrypted mother's number, present in every child's file in the databases, and leading to very few linkage failures (<2%). In our current study, the exposed group consisted of children born to women with SLE, and the control group included children born to women without SLE.

Outcome Assessment

The cohort interval for the children spanned from birth to the first of the following: end of eligibility for RAMQ coverage (i.e. migration from Quebec), event of interest (i.e. allergic condition), age 18 years, death, or end of study (i.e. December 31, 2009).

Allergic conditions in offspring were ascertained based on ≥ 1 hospitalization or ≥ 1 physician visit with a relevant diagnostic code of upper airway anaphylactic reaction (ICD-9 code 478.8, ICD-10 code T78.3), anaphylaxis (ICD-9 code 995.0, ICD-10 codes T78.0 and T78.2), urticaria (ICD-9 code 708, ICD-10 code L50) and allergy without other indication (ICD-9 code 995.3, ICD-10 code T78.4), and on ≥ 1 hospitalization or ≥ 2 physician visits for allergic rhinitis (ICD-9 code 477, ICD-10 code J30), asthma (ICD-9 code 493, ICD-10 codes J45 and J46) and eczema (ICD-9 codes 691.8 and 692, ICD-10 codes L20 and L23).[11,12]

Relevant Covariate Assessment

The "Institut de la statistique du Québec (ISQ)" provided data on the demographics of the parents at the time of delivery, as well as infant birth weight and gestational age. This allowed determination of small for gestational age babies (i.e. birth weight below the 10th percentile Canadian statistics for gestational age)[13] and premature births (i.e. babies born before 37 weeks gestation).

For all mothers in our study, reviewing the MED-ECHO and RAMQ data, comorbidities were identified based on ICD-9/10 codes indicating at least one hospitalization or at least two physician visits (at least eight weeks apart) for the diagnosis of interest, as per previously validated methodology.[14]

Relevant maternal medication exposures (i.e. antimalarials, corticosteroids and immunosuppressives), based on at least one prescription filled during pregnancy, were obtained through the RAMQ prescription database, but only for those who benefited from the public drug plan throughout pregnancy, which included 22% of exposed children and 21% of controls in our cohort. This is because although all residents in the province have public insurance to pay for hospital visits and physician visits, most individuals of working age in Quebec have private insurance that covers prescription medications. Only those who are unemployed or on social assistance are covered under the public drug plan.

Statistical Analyses

We performed univariate and multivariate analyses using a generalized estimating equation (GEE) method to estimate the odds ratio (OR) for the outcome of interest (i.e. allergic conditions), for children born to women with SLE, relative to the control group. We adjusted for maternal age, education, race/ethnicity, obstetrical complications, calendar year of birth, sex of the child, and maternal medication. These analyses were performed using the R software version 2.15.1 (Copyright 2012 The R Foundation for Statistical Computing).

Since urticaria might be induced by non-allergic etiologies (e.g. viral infection) and since the diagnostic code for allergy without indication might lack specificity, we performed a sensitivity analysis further excluding cases with diagnoses only based on urticaria and/or allergy without other inception, adjusting for the same relevant confounders as mentioned above.

Moreover, maternal history of allergic conditions might be considered an intermediate

variable in the causal pathway between the exposure (maternal SLE) and the outcome (allergic conditions) in the offspring. Although one should not adjust for an intermediate variable to estimate the total effect (i.e. direct and indirect effect) of an exposure on the outcome, we sought to assess the direct effect of maternal SLE (i.e. independent of maternal allergy) by performing a sensitivity analysis further controlling for maternal allergic conditions (using the same case definition as in offspring).

The study was approved by the "Commission d'accès à l'information du Québec" and the McGill University Research Ethics Board. Informed consent is not required for administrative database research in Quebec.

RESULTS

509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal SLE disease duration and mean follow-up of children were respectively 3.7 (standard deviation, SD, 4.0) and 9.1 (SD 5.8) years. Compared to control mothers, mothers with SLE were less likely to be Caucasian, had more co-morbidities and experienced substantially more obstetrical complications (Table 1). Compared to control children, SLE offspring were more exposed in utero to drugs, particularly corticosteroids and antimalarials.

As opposed to controls, children born to mothers with SLE experienced more allergic conditions [43.9% (95% CI 40.4, 47.6) versus 38.1% (95% CI 37.0, 39.1)]. In SLE offspring, apart from allergy without other indication, the most frequently observed allergic conditions were eczema (16.4%) and asthma (16.1%), while anaphylaxis was the least frequent (0.8%) (Table 2). In control children, apart from allergy without other indication, asthma (13.2%) and eczema (12.7%) were also the most frequent, while anaphylaxis was the least frequent (0.3%). When we repeated an analysis further excluding urticaria and allergy without other indication, offspring of

SLE mothers remained with an increased frequency of allergic conditions [30.2% (95% CI 26.9, 33.6) versus 24.5% (95% CI 23.7, 25.5).

In multivariate analysis (n=9212), children born to SLE mothers had an increased risk of allergic conditions versus control children (OR 1.35, 95% CI 1.13, 1.61) (Table 3). This risk was only slightly attenuated in the sensitivity analysis further excluding urticaria and allergy without other indication (OR 1.32, 95% CI 1.10, 1.59). When we repeated the multivariate analysis further controlling for maternal history of allergic conditions, we found that the independent effect of maternal SLE on the risk of allergic conditions in offspring persisted (OR 1.21; 95% CI 1.01, 1.44). In the subsample analysis further controlling for relevant maternal medications (n=1925), a trend remained for increased risk of allergic conditions for offspring of SLE mothers compared to controls. However, due to reduced sample size, the 95% CI was wider and included the null value (OR 1.48; 95% CI 0.94, 2.31).

DISCUSSION

Within a large cohort of SLE offspring, we observed that children born to SLE mothers had a slightly increased risk of allergic conditions. The effect of maternal SLE on the risk of allergic conditions was not completely explained by variables like maternal history of allergy, preterm birth or SGA babies, which are well-recognized risk factors for allergic conditions in offspring such as asthma.

These observations are consistent with the very few small observational studies previously conducted. Indeed, interviewing 26 SLE mothers concerning allergic conditions in their 36 children, *Sasai et al.* reported that the prevalence of atopic dermatitis and bronchial asthma was higher in these children (64% and 28%) than in controls (19% and 9%).^[7] Moreover, *McAllister et al.* evaluated the parent-reported prevalence of immune disorders in 154 children born to

mothers with SLE compared to 154 unexposed children and found that children in the SLE group had significantly more reports of allergies, hay fever and skin reactions.[8] In a more recent cohort study of 39 children born to 29 mothers with autoimmune diseases (65% of whom had SLE), *Sanchez-Manubens et al.*, conducting telephone surveys, reported a 20% incidence of bronchial asthma, which is higher than that described in the general pediatric population (usually around 12%).[9] In these prior observational studies and in ours, differences in the risk of allergies between SLE offspring and unexposed children could potentially be due to increased reporting by SLE mothers.

There are many strengths of our study, particularly the fact that we had a relatively large sample that was population-based. Quebec's administrative databases are a valid data source for observational studies of SLE subjects, with prior work from our group showing that our SLE case definition has a very high specificity (0.99).[10] In our estimates we adjusted the SLE effect estimate for calendar year; this was an attempt to adjust for environmental changes (eg, pollution, increase of pollen) over time.

Our study is not without limitations. Notably, in administrative databases, there are inherent source of uncertainty about case ascertainment. However, we used case definitions that have been validated in previous studies. For instance, using a case definition of at least one physician visit with an administrative data diagnosis code of asthma in children, *To et al.* reported a sensitivity and specificity of 91.4% and 82.9%, respectively, based on the diagnosis provided by expert chart review. A stricter case definition requiring more than one physician visit, like ours, would presumably further improve specificity.[15] We cannot exclude overestimation of the allergic cases of angioedema, urticaria and allergy without other indication given the impossibility to discern between their different etiologies (e.g. viral versus IgE-mediated) using diagnostic codes. Nevertheless, when we repeated the multivariate analysis excluding urticaria

and allergy without other indication, we still noted an increased risk of allergic conditions in SLE offspring.

Our 95% CI interval for the adjusted effect estimates of both preterm birth and SGA overlap with 95% CI of effect estimates observed in prior studies.[6] As important variables were included in our model, we might have lacked power to precisely estimate the risk of preterm birth and SGA on the outcome. In addition, the association of preterm birth with allergic conditions has been mainly established with extreme preterm birth (defined as less than 28 weeks).[6] For the purpose of our study, preterm birth was defined as less than 37 weeks of gestation.

We had information on *in utero* drug exposures only in the subsample of children with maternal drug coverage throughout pregnancy, representing approximately 20% of the entire cohort. This reduced the power of our subsample analysis investigating the effect of *in utero* drug exposures on the risk of allergic conditions, although we still noted a trend similar to our primary analyses.

In conclusion, compared to children from the general population, children born to women with SLE may have a slightly increased risk of allergic conditions. Our observations seem to be independent of obstetrical complications and maternal history of allergic conditions. Genetics, shared environmental exposures, as well as *in utero* exposure to maternal autoantibodies and cytokines might be at play and further research is needed to evaluate their potential contribution.

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Table 1. Characteristics of the cohort (n=9212)

Characteristics	SLE offspring (n=719)	Control children (n=8493)
<i>Maternal characteristics</i>		
Mean age, years (sd)	30.2 (5.1)	30.3 (5.0)
Mean education, years (sd)	14.0 (3.1)	13.8 (3.1)
Marital status, n (%)		
Couple	576 (80.1)	6904 (81.3)
Single	50 (7.0)	523 (6.2)
Unknown	93 (12.9)	1066 (12.6)
Comorbidities, n (%)		
Hypertension	47 (6.5)	85 (1.0)
Asthma	38 (5.3)	238 (2.8)
Diabetes	23 (3.2)	144 (1.7)
Depression	11 (1.5)	34 (0.4)
<i>Paternal characteristics</i>		
Mean age, years (sd)	33.2 (5.8)	33.3 (5.9)
<i>Demographic characteristics</i>		
Male gender, n (%)	402 (55.9)	4374 (51.5)
Ethnicity, n (%)		
Caucasian	444 (61.8)	6225 (73.3)
Other	275 (38.2)	2268 (26.7)
<i>Obstetrical characteristics</i>		
Mean gestational age, weeks (sd)	37.7 (2.9)	38.8 (1.9)
Mean birth weight, grams (sd)	2976 (707)	3366 (567)
Birth order, n (%)		
1	308 (42.8)	2333 (27.5)
≥ 2	411 (57.2)	6160 (72.5)
Obstetrical complications, n (%)		
Preterm birth	157 (21.8)	637 (7.5)
Small for gestational age	120 (16.7)	694 (8.2)
Gestational diabetes	30 (4.2)	263 (3.1)
<i>In utero medication information</i>		
Public drug coverage, n (%)	155 (21.5)	1770 (20.8)
Corticosteroids	34 (21.9) ^a	12 (0.7) ^b
Antimalarials	25 (16.1) ^a	1 (0.1) ^b
Immunosuppressives	11 (7.1) ^a	0 (0.0) ^b
Antidepressants	11 (7.1) ^a	52 (2.9) ^b
Anticonvulsants	1 (0.6) ^a	7 (0.4) ^b

^aDenominator used for proportion is number of children born to systemic lupus erythematosus (SLE) mothers with public drug coverage during pregnancy; ^bdenominator used for proportion is number of children born to control mothers with public drug coverage during pregnancy

Table 2. Characteristics of the allergic conditions

Allergic conditions	N Frequencies (%)	1 billing only (%)	≥2 billings (%)	1 billing and hospitalization (%)	≥2 billings and hospitalization (%)	Hospitalization only (%)
Eczema						
SLE offspring	118 (16.4)		92.4	1.7	4.2	1.7
Controls	1082 (12.7)		94.2	1.8	2.1	1.8
Asthma						
SLE offspring	116 (16.1)		69.0	3.4	25.9	1.7
Controls	1123 (13.2)		69.5	6.5	22.3	1.8
Urticaria						
SLE offspring	91 (12.7)	84.6	13.2	0.0	1.1	1.1
Controls	951 (11.2)	87.6	10.4	0.7	0.4	0.8
Allergic rhinitis						
SLE offspring	19 (2.6)		100.0	0.0	0.0	0.0
Controls	189 (2.2)		97.9	0.5	0.5	1.1
Anaphylaxis						
SLE offspring	6 (0.8)	50.0	0.0	16.7	0.0	33.3
Controls	25 (0.3)	80.0	12.0	4.0	0.0	4.0
Upper airway anaphylactic reaction						
SLE offspring	3(0.4)	66.7	0.0	0.0	0.0	33.3
Controls	13(0.2)	84.6	7.7	0.0	0.0	7.7
Allergy without other indication						
SLE offspring	119 (16.6)	78.2	21.0	0.8	0.0	0.0
Controls	1238 (14.6)	83.8	15.6	0.2	0.1	0.4

Table 3. Univariate and multivariate analyses of the risk of allergic conditions (SLE offspring versus controls) (n=9212^b)

Covariates	Univariate OR ^a for allergic conditions (95% CI)	Primary multivariate OR ^a for allergic conditions (95% CI)
Maternal SLE		
No	Reference	Reference
Yes	1.33 (1.12, 1.58)	1.35 (1.13-1.61)
Sex of child		
Female	Reference	Reference
Male	0.88 (0.80-0.96)	0.88 (0.80-0.96)
Race/ethnicity		
Other	Reference	Reference
Caucasian	0.90 (0.80-1.01)	0.88 (0.78-1.00)
Education		
High school or less	Reference	Reference
College or more	1.01 (0.82-1.25)	1.02 (0.82-1.25)
Preterm birth		
No	Reference	Reference
Yes	1.04 (0.88-1.23)	0.99 (0.84-1.17)
Small for gestational age	Reference	
No	0.97 (0.83-1.13)	Reference
Yes		0.95 (0.81-1.11)

^aMatching and adjusting for maternal age and calendar year; odds ratio (OR); confidence interval (CI); systemic lupus erythematosus (SLE)

^b When small for gestational age is included in the model, sample size is reduced from 9212 to 9199