Reproductive issues in women with systemic lupus erythematosus: should we be afraid of the Big Bad Wolf?

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Abstract/Résumé

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder, which can affect almost any organ system and may even be life-threatening. SLE predominantly affects women during their reproductive years, with a prevalence of approximately 1.5/1000 in women of 18-44 years, and is associated with significant morbidity during pregnancy.

Many women with SLE ask if the disease will impair their capacity to have children and affect the long-term health of their offspring. Studies assessing these issues are scant and limited by methodological considerations. The first two manuscripts in this thesis present relevant literature reviews.

The objectives of this doctoral research were to fill this knowledge deficit by first assessing live births in women with SLE. We conducted two studies estimating live birth rates in women with SLE using standardized incidence ratios (SIR) with general population rates as a reference. Both studies had very different study populations: one relied on an international inception cohort of women with SLE (manuscript #3), the other on an SLE cohort derived from Quebec's administrative databases (manuscript #4). This allowed us to investigate different aspects and predictors of live birth rates in women with SLE. Then, to answer the second research question, we determined if maternal SLE influences the long-term health of the offspring. To do so, we performed two studies within a large population-based cohort of children born to SLE women, the "Offspring of SLE mothers Registry (OSLER)", which we specifically created for this thesis research. These studies respectively evaluated the risk of congenital heart defects (manuscript #5) and autism spectrum disorders (manuscripts #6) in SLE offspring compared to children from the general population.

This doctoral research provides novel and much-needed information, which will help physicians provide adequate counseling to women with SLE contemplating pregnancy. We conclude this thesis by discussing potential future directions of additional studies on reproduction in women with SLE and health outcomes in their offspring.

Le lupus érythémateux disséminé (LED) est une maladie auto-immune chronique, qui peut toucher presque tous les organes du corps, menaçant parfois la vie des patients atteints. Le LED affecte de façon prédominante les femmes en âge de procréer, ayant une prévalence approximative de 1.5/1000 femmes de 18-44 ans, et est associé à une morbidité significative en grossesse.

Plusieurs femmes atteintes de LED demandent si la maladie va diminuer leur capacité à avoir des enfants et influencer la santé à long terme de leurs enfants. Peu d'études adressent ces problématiques et sont limitées dans leur méthodologie. Les deux premiers manuscrits de cette recherche doctorale présentent une revue de la littérature pertinente à ce sujet.

Les objectifs de cette thèse étaient de répondre à ce défaut de connaissance, en commençant, premièrement, par évaluer les naissances vivantes survenant chez les femmes avec LED. Pour ce faire, nous avons effectué deux études estimant les taux de naissances vivantes chez des femmes avec LED, au moyen d'un ratio d'incidence standardisé, en utilisant les taux de la population générale comme référence. Ces deux projets comprenaient des populations très différentes: une étude se reposait sur une cohorte internationale de femmes avec LED (manuscrit #3), l'autre sur une cohort de femmes avec LED dérivée des banques de données administratives du Québec (manuscrit #4). Ceci nous a permis d'investiguer différents aspects et prédicteurs des taux de naissances vivantes chez les femmes avec LED. Ensuite, afin de répondre à notre deuxième question de recherche, nous avons déterminé si le LED maternel influençait la santé à long terme des enfants nés de mères atteintes. Pour ce faire, nous avons réalisé deux études à l'intérieur d'une grande cohorte populationnelle d'enfants nés de mères avec LED, la cohorte OSLER ("Offspring of SLE mothers Registry"), que nous avons spécifiquement créée pour cette recherche doctorale. Ces études évaluaient respectivement le risque de malformations cardiaques

congénitales (manuscrit #5) et le risque de désordres du spectre de l'autisme (manuscrit #6) chez les enfants de femmes avec LED comparés aux enfants de la population générale.

Cette recherche doctorale génère de l'information nouvellle, originale, et nécessaire, qui aidera les cliniciens à conseiller adéquatement les femmes avec LED qui contemplent une grossesse. Nous concluons cette thèse en discutant de directions potentielles et futures d'études additionnelles sur les problématiques de la reproduction des femmes avec LED et de l'état de santé à long term de leurs enfants.

Preface

" Once upon a time there lived in a certain village a little country girl, the prettiest creature who was ever seen. Her mother was excessively fond of her (...). This good woman had a little red riding hood made for her. It suited the girl so extremely well that everybody called her Little Red Riding Hood." Charles Perrault, Tales of Mother Goose, Paris 1697.

There is no better tale than "Little Red Riding Hood" to symbolize this thesis. First, "lupus" is the latin word for wolf. Moreover, the synopsis of this classical bedtime story involves a Big Bad Wolf who eats alive a maternal figure to subsequently endanger the life of her progeny. Finally, according to the different story versions, there might be hope at the end. In the Grimms Brothers' version, a drastic intervention by a third party saves both the woman and the child, leaving the Big Bad Wolf defeated.

The word "lupus" as a designation for this disease comes from the skin lesions frequently seen in SLE, which were initially described to look like "wolf bites". These skin lesions were the first SLE clinical manifestation to be described. Interestingly, Sir William Osler, one of the most famous McGill alumni, has been the first to recognize that lupus cutaneous lesions could be associated with systemic manifestations, hence the name "systemic lupus erythematosus".

Known as one of the greatest physicians of all time, Osler received in 1872 his medical degree from McGill, where he was appointed a professor of medicine. In recognition of his contribution to the Department of Medicine, the Montreal General Hospital amphitheatre bears his name. Similarly, I thought that there was no better acronym to represent the large population-based cohort at the centre of this thesis, the "Offspring of SLE mothers Registry (OSLER)".

This is nothwithstanding that each time I come to work at the Montreal General Hospital Lupus Clinic, I meet the staring eyes of Sir William Osler's portrait aside the amphitheatre,

which is steps away from the clinic. When our eyes meet, I always wonder what motivated him to become a physician. This thought inevitably makes me think about why I've become a rheumatologist and embarked in a PhD in epidemiology, with the desire to further study SLE.

My interest and fascination for SLE go back to how I came in contact, for the first time, with this condition. As a medical student, the first patient I ever took care of suffered from SLE. And here, the word "suffered" has all its meaning. She was a 50-year-old woman who had developed SLE during early adulthood. Her disease had been severe, with multiple episodes of flare, leaving her with several sequelas. Notably, because of antiphospholipid autoantibodies associated with her SLE, her right leg had thrombosed and had been amputated. As most of her disease complications had already manifested when she was a young adult and had impaired considerably her life, she never married and never had children.

When I met her, she was hospitalized to undergo a cardiac surgery for a severe aortic stenosis, which was another SLE complication and caused her to have unstable angina. Before the procedure, she had to go through several investigations and was therefore admitted for two weeks. During these weeks, I learned to know her and appreciated how much the disease had impacted her life.

The last investigation required before her surgery was a cardiac catheterization. The day after this test, when I went to see her, something was wrong. She was experiencing more angina than usual and was on the edge of fainting. While I was calling for help, she kept telling me not to let her die. Just as we transferred her to the intensive care unit, she went into cardiac arrest and died.

Her death was later found to have been caused by an internal bleeding, due to the catheterization procedure. She was particularly at risk for this complication, as she was

anticoagulated for her prior thrombotic event. I was shocked by the chain of events. Not only because she literally died in my hands, but also because I realized how much the disease had poisoned her life, up to the end. Her life had been SLE: a pervasive, chronic, often disabling, and occasionnally fatal disease, mostly affecting women in their childbearing years. She was the prototypic patient.

This woman and her condition made a big impression on me, as I was a medical student. Since then, I have always remained intrigued by this fascinating autoimmune disease. It is therefore very gratifying to try to better understand it through research, and this PhD thesis is a humble attempt at it.

Acknowledgements

I have been extremely priviledged to have as mentors, two accomplished researchers, dedicated clinicians, incredible women, and mothers, Drs Sasha Bernatsky and Ann Clarke.

I am particularly grateful to Sasha, my supervisor, who has always been there for me. There is no doubt that without her generous support and endless patience this thesis would not have existed. Her committment to help me succeed in my career have provided me with the best mentorship that I could have wished for. I will always be in debt to her.

I am also extremely thankful to Dr Robert Platt, my co-supervisor, who enriched my learning process with his invaluable statistical expertise. In addition, I would like to thank Dr Lawrence Joseph, who enlighted me on some aspects of Bayesian statistical modeling.

A special thank to Dr Christian Pineau, my "work brother", who has been very supportive of both my clinical and research work in SLE.

I would like to thank Dr Caroline Gordon, who sparked my interest to study long-term outcomes in SLE offspring.

I would like to acknowledge all the excellent work of the support staff from the Division of Clinical Epidemiology (Jennifer Lee, Autumn Neville, Susan Scott, Yvan St-Pierre, Jeremy Labrecque, Mary Ford). Similarly, I would like to thank the dedicated support staff of the Department of Epidemiology, as well as its fantastic teachers and researchers.

I am grateful to my parents, Aline and Bernard, for their support and their love. They have made who I am. Their accomplishements have set an example for me that I aspirate to emulate.

I would also like to acknowledge the infinitissimal patience of my husband, Sarto. A gastro-enterologist, who heard more about epidemiology and SLE over the past 7 years than he

would have ever wished for. I thank him for his love, infallible support, and unalterable belief in me.

Finally, I dedicate with love all the work poured into this thesis to Capucine and Éloïse, my daughters. They know nothing about a PhD thesis and (right now at least) they couldn't care less, but they have been my inspiration and my comfort at difficult times, helping me to put everything into perspective. Both Capucine and Éloïse were born into this thesis, and both love story telling, such as the Little Red Riding Hood...

Contribution of Authors

Manuscript #1.

Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. Systemic lupus erythematosus in women: impact on family size. Arthritis Rheum. 2008 Nov 15;59(11):1656-60.

The idea behind this review originated from both Dr Bernatsky and myself. I performed the review of the literature and drafted the first version of the manuscript. Drs Clarke and Bernatsky provided important suggestions for revision. All authors were involved in revising the article for important intellectual content.

Manuscript #2.

Vinet E, Pineau CA, Clarke AE, Fombonne É, Platt RW, Bernatsky S. Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus. Lupus. 2014 Oct;23(11):1099-104.

I conceived of the idea behind this manuscript, performed the review of the literature, and drafted the first version of the manuscript. Dr Bernatsky provided important suggestions for revision. All authors were involved in revising the article for important intellectual content.

Manuscript #3.

Vinet E, Clarke AE, Gordon C, Urowitz MB, Hanly JG, Pineau CA, Isenberg D, Rahman A, Wallace D, Alarcón GS, Bruce I, Petri M, Dooley MA, Kalunian K, Maddison P, Aranow C, van Vollenhoven R, Bernatsky S. Decreased live births in women with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2011 Jul;63(7):1068-72.

The methodology used in this study was based on previous work from our group. I conceived of the study idea. I elaborated the study objectives and protocol, as well as conducted the statistical analyses, interpreted the results, and drafted the manuscript. The dataset was assembled by the Systemic Lupus International Collaborating Clinics (SLICC) members (Clarke, Gordon, Urowitz, Hanly, Isenberg, Rahman, Wallace, Alarcón, Bruce, Petri, Dooley, Kalunian, Maddison, Aranow, van Vollenhoven, Bernatsky). Dr Bernatsky reviewed the protocol and critically revised the manuscript. Yvan St-Pierre provided technical support for the statistical analyses. All authors reviewed the final version of the manuscript.

Manuscript #4.

Vinet E, Labrecque J, Pineau CA, Clarke AE, St-Pierre Y, Platt R, Bernatsky S. A population-based assessment of live births in women with systemic lupus erythematosus. Ann Rheum Dis. 2012 Apr;71(4):557-9.

This study was an extension of the work performed in the preceding manuscript. I conceived of the study idea. I elaborated the study objectives and protocol, as well as conducted the statistical analyses, interpreted the results, and drafted the manuscript. Data were obtained by Dr Bernatsky. Yvan St-Pierre and Jeremy Labrecque offered technical support for the statistical analyses. Drs Platt and Bernatsky provided guidance for the statistical analyses. All authors were involved in revising the article for important intellectual content.

Manuscript #5.

Vinet E, Pineau CA, Scott S, Clarke AE, Platt RW, Bernatsky S. Increased Congenital Heart Defects in Children Born to Women with Systemic Lupus Erythematosus: Results from the

Offspring of Systemic Lupus Erythematosus Mothers Registry Study. Circulation. 2015 Jan 13;131(2):149-56.

I conceived of the study idea. I elaborated the study objectives and protocol, obtained the data, and constructed the dataset. I conducted the statistical analyses, interpreted the results, and drafted the manuscript. Dr Bernatsky helped me in obtaining respectively the data from the "Régie de l'assurance maladie du québec (RAMQ)" and necessary approvals from the "Commission d'accès à l'information (CAI)". Susan Scott offered technical support for the construction of the dataset and statistical analyses. Drs Platt and Bernatsky provided guidance for the statistical analyses. All authors were involved in revising the article for important intellectual content.

Manuscript #6.

Vinet E, Pineau CA, Clarke AE, Scott S, Fombonne É, Joseph L, Platt R, Bernatsky S. Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: results from the OSLER cohort. Arthritis Rheum. February 2015 (under review)

I formulated the study idea. I elaborated the study objectives and protocol, obtained the data, and constructed the dataset. I conducted the statistical analyses, interpreted the results, and drafted the manuscript. Dr Bernatsky helped me in obtaining respectively the data from the RAMQ and necessary approvals from the CAI. Susan Scott offered technical support for constructing the dataset. Dr Lawrence Joseph provided technical help for the conduct of the Bayesian latent class analyses. Drs Platt and Bernatsky provided guidance for the overall statistical analyses. All authors were involved in revising the article for important intellectual content.

Statement of Originality

This doctoral thesis provides a number of original contributions to reproductive issues in women with SLE, in addition to providing relevant literature reviews. We are the first to demonstrate an important reduction in live birth rates in SLE women compared to the general population, particularly after SLE diagnosis, using standardized incidence ratios. In addition, we investigated potential predictors of live births in women with SLE and demonstrated that prior hospitalization for SLE was an important predictor of reduced live births.

Moreover, using Quebec's administrative databases, we have assembled the world's largest cohort of children born to mothers with SLE, the "Offspring of SLE mothers Registry (OSLER)", which provides, with its large sample size and historically prospective cohort study design, a unique opportunity to assess rare long-term health outcomes in SLE offspring. Using this innovative data source, we are the first to establish a substantially increased risk of autism spectrum disorders in SLE offspring compared to children from the general population. We used Bayesian latent class models to account for imperfect autism spectrum disorders case ascertainment in administrative data.

Furthermore, we are the first to demonstrate a substantially increased risk of congenital heart defects and cardiac repair procedures in children born to SLE mothers compared to children from the general population. We accounted for detection bias due to differential screening with fetal echocardiography by excluding children undergoing at least one fetal echocardiography. We carefully considered the potential for unmeasured confounding by performing relevant sensitivity analyses.

In all these studies, we used appropriate statistical methods (such as Huber-White correction, generalized estimating equations, and random effect models) to account for correlation in reproductive outcomes.

I attest that the work included in this thesis is original and take full responsability for the accuracy and completeness of the data.

Statement of Financial Support

My PhD studies and the work related to this thesis were funded through a Canadian Institutes of Health Research (CIHR) Clinical Research Fellowship Award (2007-2012) and a "Fonds de Recherche en Santé du Québec" Fellowship Award (2012-2015). In addition, the research project pertaining to manuscript #5 was funded by the CIHR operating grant entitled "Obstetrical and long-term outcomes in children born to women with SLE", while the sudy related to manuscript #6 was funded by the CIHR operating grant "Neurodevelopmental disorders in children born to women with SLE". I was principal investigator (with Dr Bernatsky as the nominated principal investigator) on both of these operating grants and actively took part in securing this funding.

Table of content

1. Introduction

SLE is a chronic autoimmune disorder, which can affect almost any organ system and may be life-threatening.[1] Thus, although a relatively rare condition (with prevalence estimates of about 1.5 in 1000 females of 18-44 years), SLE is an important cause of morbidity and mortality.[2] SLE predominantly affects women during their reproductive years, and is associated with a well-established increased risk of complications during pregnancy.[3]

Many women with SLE ask if the disease will affect their capacity to have children. Studies assessing the impact of SLE on family size are scant and limited by methodological issues.[4-6] However, multiple disease-related factors may limit the number of children born to women with SLE. These factors potentially include decreased fertility, adverse pregnancy outcomes (e.g., miscarriages, stillbirths), relative contraindications to pregnancy (e.g., high disease activity or dependence on a teratogenic medication), impaired sexual function and/or personal relationships, or a deliberate decision to limit family size.

Indeed, many women with SLE see their disease as a barrier to childbearing, partly due to the fear that it will affect the health of their children.[7] Even if the pregnancy is successful, women with SLE are concerned that other complications will affect their children. It is very hard to give evidence-based counseling on the health outcomes of their children, outside of pregnancy complications.

Only a few studies have assessed long-term outcomes in the offspring of mothers with SLE. A handful have examined issues such as learning disabilities and/or attention deficit disorder, by using questionnaire methodology in small samples (N=47-116 children), showing a potentially increased risk.[8-12] In addition, there is only very limited data on congenital anomalies in SLE offspring.

Therefore, two important questions on reproductive health in women with SLE remain unanswered, namely: 1) Does SLE limit the number of children born to affected women? and 2) Does maternal SLE affect the health of the offspring outside of pregnancy complications? These two questions are intimately related as their answers will allow appropriate counseling of women with SLE contemplating pregnancy. The first two manuscripts in this thesis provide relevant literature reviews.[13,14]

The objectives of this thesis were to address these important issues by first assessing live births in women with SLE. We present two studies that we published, estimating live birth rates in women with SLE using standardized incidence ratios (SIR) with general population rates as a reference.[15,16] Both studies had very different study populations: one relied on an international inception cohort of women with SLE (manuscript #3), the other on a SLE cohort derived from Quebec's administrative databases (manuscript #4).[15,16] This allowed us to investigate different aspects and predictors of live birth rates in women with SLE.

Then, to answer the second research question, we determined if maternal SLE influences the health of the offspring, aside from the well-recognized fetal and neonatal outcomes related to pregnancy complications. To do so, we performed two studies within a large population-based cohort of children born to SLE women, the "Offspring of SLE mothers Registry", which we specifically created for this thesis research.[17,18] These studies respectively evaluated the risk of congenital heart defects (manuscript #5) and autism spectrum disorders (manuscript #6) in SLE offspring compared to children from the general population.[17,18]

This thesis research provides novel and much-needed information for women with SLE, their families, and the physicians who care for this population. We will conclude this thesis by

discussing potential future directions of additional studies on reproduction in women with SLE and health outcomes in their offspring.

2. Literature review

2.1. Potential impact of maternal SLE on live births

2.1.1. Preamble to manuscript #1

SLE is a multi-system autoimmune disease, characterized by a dysregulated immune system, resulting in widespread organ inflammation and damage.[19] It generally begins at/or after puberty, with the highest incidence in women during the reproductive years.[1] SLE can cause considerable morbidity and mortality, with current 10-year survival figures of about 85%.[20-22] Depending on organ involvement, treatment may include corticosteroids, such as prednisone, and immunomodulating agents, such as antimalarial drugs and immunosuppressives. Other drugs may be required to prevent or treat the many conditions that often arise during the course of SLE, including hypertension, depression or seizures. There is currently no cure for SLE, and the life-time course is characterized by periods of disease flare and sometimes, remission.[19]

Until about 20 years ago, women with SLE were often recommended to avoid pregnancy because of the potential for pregnancy-related disease flares, thrombotic events, hypertension, pre-eclampsia, and diabetes in the mother during pregnancy.[23-29] In SLE pregnancies, there has traditionally been concerns regarding miscarriage, stillbirth, low birth weight, preterm birth, and neonatal death, particularly in women with antiphospholipid antibodies, renal disease, or hypertension.[30-33] However, with modern management, currently many women with SLE can have successful pregnancies, albeit with close monitoring and appropriate preventive therapies.[34]

Yet, upon being diagnosed with SLE, women of childbearing age might wonder if the disease will limit their ability to have children. Until now, research has focused on studying the proportion of SLE pregnancies ending in live births. However, aside from pregnancy

complications, such as miscarriages and stillbirths, there might be several other ways by which SLE could negatively influence the number of live births in affected women. In manuscript #1, we discuss the multiple disease-related factors that might limit live births in women with SLE, and we provide a comprehensive review of the literature on this subject.[13] This manuscript, entitled "Systemic lupus erythematosus: impact on family size", was published in Arthritis Care & Research (2008; 59:1656-60). A reprint of this article is included in Appendix F.

2.1.2. Title page

Title: Systemic Lupus Erythematosus in Women: Impact on Family Size

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2.1.3. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease often affecting women in their reproductive years. Upon diagnosis, these women are faced with a life-long illness that may have considerable impact not only on their physical health, but also on their existing family and/or reproductive potential. With recent advances in the management of this condition, it is hoped that good disease control can be achieved in the majority of cases, and thus most of these women are not advised against pregnancy. However, multiple disease-related factors may still affect the number of children born to women with SLE.

Several studies have investigated the influence of SLE on reproduction and family size.[4-6] A study by Hardy et al. showed that Caucasian women with SLE appeared less likely than controls to have more than two children (OR 0.56 ; 95% CI 0.31-1.03).[4] In a population-based study of women with rheumatic diseases, a lower number of births (mean 1.7; 95% CI 1.5-1.9 versus controls 2.2 , 95% CI 2.1-2.3) and a reduced period of reproduction were observed in women with connective tissue diseases (CTD), including SLE, compared to healthy controls.[5] The inter-pregnancy interval was longer and the proportion of women achieving a subsequent pregnancy was reduced in women with CTD.

However, these findings may not be specific for SLE. Similar data were shown in women with rheumatoid arthritis (RA).[35] Women diagnosed prior to the birth of their first child had fewer pregnancies and children. Twenty percent reported that RA had affected their decision to have children or decision about family size.[35] The disease aspects most commonly reported to affect childbearing decisions were concerns about being able to care for a child, medication issues (including fear that medication would affect the fetus and concerns about stopping medication), as well as fears that their own children may eventually develop the disease.

2.1.4. Childbearing decision

Several characteristics of the disease are to be considered before planning pregnancy in women with SLE, and these may impact on their capacity and decision to have children. Although still controversial, there is a probable increased risk of flare during pregnancy and in the postpartum period. Several small studies found no significant increase in SLE activity during pregnancy.[36-39] However, more recent studies have found a two- to three-fold increase in SLE activity during pregnancy.[27,40-42] Based on these studies, between 35% and 70% of all pregnancies will have measurable disease activity, with most studies showing the risk to be between 40% and 50%.[38-41] The risk for a moderate to severe flare is lower and ranges between 15% and 30%.[29,43,44] Recent data have demonstrated the absence of fetal toxicity of hydroxychloroquine (HCQ) use throughout pregnancy. As HCQ discontinuation is associated with an increased risk of flare in pregnant and non-pregnant patients, and since it is no longer contraindicated during pregnancy, it is likely that the risk of disease flare in pregnancy will be reduced.[45-47] Nevertheless, disease exacerbation can occur at any time during pregnancy, as well as several months after delivery. Women with no or mild disease activity in the 6 months preceding pregnancy are less likely to experience disease exacerbation.[3] For this reason, women are generally recommended to have stable disease for 6 months before conceiving. This potentially could retard motherhood or increase the interval between pregnancies in some women.

Pregnant women with SLE are at increased risk of miscarriage or stillbirth. Approximately 20% of pregnancies in women with SLE will end in a miscarriage (a pregnancy

loss before 20 weeks gestation), as compared to 9% in the general population.[4,48] Some studies have demonstrated that this risk was present even before SLE diagnosis, with almost a two-fold increase compared to controls (OR 1.99; 95% CI 1.28-3.10).[4] The risk of stillbirth (a pregnancy loss after 20 weeks gestation) has also been shown to be elevated in several studies, with approximately a three-fold increase compared to the general population.[27] The two most important risk factors for pregnancy loss are increased lupus activity and antiphospholipid syndrome.[48] Obviously, miscarriages and stillbirths may directly contribute to a reduction in family size.

In addition, SLE is associated with an increased risk of maternal complications during pregnancy, including pregnancy-induced hypertension, pre-eclampsia and thrombo-embolic events.[3] Pre-eclampsia complicates 5% to 8% of pregnancies in the general population.[3] However, the rate of pre-eclampsia ranges from 13% to 35% in women with SLE.[29,48-50] Pre-eclampsia can lead to significant complications, which include preterm birth, stroke and even death.[3]

Furthermore, certain drugs used to treat SLE manifestations, such as methotrexate and cyclophosphamide, are contraindicated during pregnancy because of potential fetal harm.[51] Recently, mycophenolate mofetil, a relatively recent addition to the treatment of SLE, has been shown to be potentially associated with a specific pattern of congenital malformations, which notably includes cleft lip and palate, microtia, micrognathia and hypertelorism.[52-55] These medications must be stopped or switched to safer ones in prevision of the conception. This requires planning under health care professional supervision. Dependence on a medication in order to maintain disease control may delay pregnancy in some patients.

Moreover, future mothers might be worried that their children may be affected by SLE, even if this risk is small. There is evidence that SLE occurrence is increased in the offspring of patients with SLE; lupus prevalence has been estimated at about 4% in the children of parents with SLE.[56] Other studies reported that up to 12% of SLE patients had first-degree relatives with SLE or other connective tissue diseases.[57] Other autoimmune diseases, such as autoimmune thyroid disease, are also more common in first-degree relatives, including children of patients affected from SLE.[58] There is some evidence that the disease onset may be earlier in the child than in the affected mother, representing a general phenomenon reported in genetically transmitted diseases.[58]

As a result of drug exposure, maternal disease activity or complications, the baby may be born prematurely, suffer from low birth weight and intra-uterine growth retardation (IUGR). Estimates of the number of lupus pregnancies that end in premature delivery (delivery before 37 weeks gestation) have ranged widely, between 10-50%; higher estimates may relate to sicker patients seen in tertiary care centers.[3] In a population-based study of 555 SLE deliveries in the United States, 21% were preterm, which corresponded to approximately a two-fold higher rate than in healthy women.[28] In general, premature babies have an increased risk of respiratory complications, infections, developmental abnormalities (especially neurological), and death in the neonatal period.[59]

On average, about 10% of all SLE births are small for gestational age (SGA) (weight below the 10^{th} percentile for gestational age), comparable to what would be expected in the general population.[3] Some cohorts, however, report increased rates as high as 35%; the higher figures may again relate to sicker SLE patients from tertiary care centers.[29,40,48] In the general population, there is some evidence that children of low birth weight and IUGR may be at

risk of juvenile-onset diabetes mellitus, early-onset hypertension (for example, in adolescence), and premature coronary artery disease.[60-63] In the offspring of SLE mothers, some studies have suggested an increased risk of learning disabilities (incidence of 20-30%), particularly in boys.[8-11] However, most of these studies relied on self-report, which could have biased the estimates. Only limited data are available on the long-term outcomes of children born to mothers with SLE.

Faced with the potential risks of disease flare and/or adverse maternal and fetal outcomes, and considering the additional demands (physical, social, and emotional) related to the management of SLE, some women may choose not to have children. In a study assessing social functioning in 114 SLE females, 49% had children, 32% planned to have a child or another child, 18% planned no children and 1% were undecided. SLE was viewed as a barrier to childbearing by 27%.[7] Common concerns included worries that pregnancy might exacerbate the disease, that medications or the disease might harm the fetus, and that the disease might interfere with childcare. In another study addressing disease impact on family planning in 40 females having children after SLE diagnosis, 45% of women reported anxiety about pregnancy, in most cases relating to the fear of transmitting the disease to their offspring.[64] In addition, 23% considered that SLE interfered with their ability to attend to their family.

2.1.5. Personal relationship and sexuality

Sexual function is impaired in women with SLE.[65] The disease can affect sexual function in different ways. Physical problems, such as chronic pain and fatigue, and emotional problems, such as low self-esteem and depression, can decrease a patient's sexual interest and reduce intercourse frequency. Disturbances of hormonal status by corticosteroid treatment and disease

activity can reduce libido and interfere with successful reproduction.[66] Partnership difficulties arising from disease-related stress can also contribute to a less active sexual life.[67] In a study by Boomsma et al., 20% of SLE patients thought that their illness had driven their family apart or worsened their relationship with their partner.[68]

The impact of SLE on sexuality is not necessarily addressed by health care professionals, and is not part of questionnaires used routinely to assess physical function or quality of life in lupus populations.[66] A recently validated disease-specific health-related quality of life instrument, the LupusQuol, assessed intimate relationships, and patients who were asked for feedback thought it was an important aspect of the questionnaire.[69] Patients and health care professionals may be reluctant to discuss the issue, even when there is marked impairment of sexual function.[66] This miscommunication was highlighted in a study of 74 RA patients where only one patient reported being asked if the disease had caused any sexual problems.[70] Most sexually active SLE females have problems with sexual function when acutely ill.[57] Disease intrusiveness on sexuality does not seem to differ between males and females in subjects with RA, but this has not been assessed in SLE patients.[71] Understanding and support during lupus exacerbations has been cited as the most important factor leading to an adequate sexual lifestyle adjustment.[57] Thus, health care providers should be aware of how SLE can interfere with the relationships of their patients, and affect sexuality. The health care provider can also help by encouraging communication between the patient and significant others, and by providing information on how the disease and its therapy can affect a patient's sexual life. Consultation with specialists may be helpful; for physical factors, a gynecology opinion may be helpful; for psychological issues, psychotherapy may be useful.

2.1.6. Fertility

In women with SLE, fertility might be impaired due to associated autoimmune anomalies, therapy (i.e. cyclophosphamide) and hormonal dysfunction (i.e. transient amenorrhea). Antiphospholipid (aPL) antibodies are known to be associated with pregnancy losses.[72] Murine studies suggest that aPL antibodies induce pregnancy loss through disruption of placental circulation and could also interfere with implantation of the embryo.[73] However, the role of aPL antibodies in infertility and in vitro fertilization (IVF) failure is still controversial in humans. Several retrospective studies have shown a positive association between aPL antibodies and IVF failure, while prospective studies, the largest assessing 793 women, have not confirmed this.[74,75] The underlying mechanisms by which aPL antibodies impair reproductive function are still obscure.

Although it is unclear if the disease itself is associated with infertility, some drugs used in its treatment might cause infertility that is either reversible (i.e. non-steroidal anti-inflammatory drugs, NSAIDs) or potentially irreversible (i.e. cyclophosphamide).[66] Prostaglandins, inhibited by NSAIDs, are involved in ovulation and implantation. Several case reports and small series of women with rheumatic diseases have described transient infertility following treatment with NSAIDs, including indomethacin, diclofenac, and naproxen.[76,77] Animal and human studies have shown that NSAIDs can inhibit rupture of the luteinized follicle, which can cause infertility.[66,78] However, the magnitude of this adverse effect has not been established at the present time.

Premature ovarian failure has been observed after treatment with alkylating agents such as cyclophosphamide. The gonadal toxicity of cyclophosphamide is related to cumulative dose, administration route and age at treatment onset.[79] Women under the age of 26 years are less

likely to develop ovarian failure than those who started treatment at a later age.[80] The frequency of premature ovarian failure due to cyclophosphamide varies from 11 to 59%.[79] A recent study showed that treatment with synthetic Gonadotropin Releasing Hormone (GnRH), while receiving cyclophosphamide treatment, significantly reduced the risk of premature ovarian failure.[81] Only 5% of the GnRH-treated group developed ovarian failure compared to 30% in the control group.[81]

Moreover, menstrual irregularities and anovulatory cycles have been reported in patients with active disease and in those treated with high dose corticosteroids.[82] End-stage renal failure secondary to lupus nephritis can also result in amenorrhea.[83]

Although fertility might be impaired in several ways, there is a general notion that SLE does not diminish fertility in affected women. However, this aspect of reproduction in SLE has never been measured adequately. Most authors cite a study done in 1974 by Fraga et al., which reported a fertility rate in women with SLE comparable to an age-matched control group of healthy women.[6] However, the fertility rate was calculated using the number of pregnancies in women who had at least one pregnancy. This overestimated the number of pregnancies per women with a diagnosis of SLE, as those who did not achieve any pregnancy were excluded. In this study, a total of 79 SLE women and 80 healthy subjects with a mean age of 33.1 years (range 17-62 years) were evaluated.[6] There were a total of 183 pregnancies among 53 patients before the clinical diagnosis of SLE, which resulted in 42 spontaneous abortions and 141 live births. In the remaining 26 SLE patients, no pregnancy occurred. Forty-two pregnancies occurred in 20 patients after the onset of SLE, while 33 women did not become pregnant again. Of the 42 pregnancies, 17 ended in spontaneous abortions and 25 in live births. In 24% of the 26 women who did not have further pregnancies, the only associated factor appeared to be disease

activity. In the control group, 288 pregnancies occurred in 80 women, resulting in 252 live births. Thus in fact, these results raise the possibility that fertility rate and birth rate might be reduced in SLE women, particularly after diagnosis.

One difficulty in assessing fertility in women with SLE is the lack of consensus on the definition and measurement of fertility. Demographic studies generally define fertility rate as the number of live births per 1000 women of reproductive years (usually between 15-44 years) in a given year.[84] From this rate, a synthetic fecundity index is generally derived in demographic studies to estimate the mean number of children that a woman would have if her fertility rate, during her entire life, followed the same rate as reported for her population age group.[84] These measures are useful for large population studies, but would be difficult to apply for the study of SLE women, in order to allow comparison with population figures.

Some refer to fertility as the absence of infertility, which itself is usually defined as the inability of a couple of reproductive age to establish a pregnancy, by having regular sexual intercourse, within one year.[85] To date, no study has attempted to measure the prevalence of infertility in SLE women by using this widely accepted definition. There is also no information on the time to conception in SLE. This represents an important deficiency, as these data are necessary to counsel women with SLE regarding their childbearing capacities.

2.1.7. Conclusion

Although most women with SLE would like to have children,[86] some studies have shown a reduction in their family size.[4,5] Many factors (both physical and psychosocial) may influence childbearing decisions and the capacity to have children. The relative importance of these factors may vary according to disease activity, damage, and/or treatment. More studies are needed to

evaluate how SLE affects reproduction, particularly the extent to which fertility is altered in women with SLE.

2.1.8. Supplemental material to manuscript #1

As mentioned previously, childbearing decision, and hence live birth rates, in women with SLE might be influenced by the fear that the disease will affect the health of the offspring. To date, research has focused on studying pregnancy complications in women with SLE, as opposed to investigating offspring health outcomes. Thus, little is known about the long-term effect of maternal SLE, its complications, and its treatments on the children born to affected mothers.

2.2. Congenital heart defects (CHD) in SLE offspring

2.2.1. CHD overview

As a result of drug exposure, maternal SLE disease activity, or autoimmunity, babies may face adverse health outcomes.Within the general population, congenital anomalies are relatively common, occurring in approximately 3% of births.[87] Thus, it is not surprising that women with SLE often worry about congenital anomalies being a potential complication.

Congenital heart defects (CHD) are the most frequent of these events, accounting for approximately a third of all congenital anomalies;[88] they are associated with substantial child morbidity.[89] In utero exposures, such as maternal illnesses and medications, are thought to play an important role in the yet to be fully elucidated etiology of CHD.[90,91] In particular, a recent study suggests a 3-fold increased risk of CHD in children born to mothers with various systemic connective tissue disorders, including SLE.[91] However, the investigators did not specifically assess the SLE effect estimate for the risk of CHD and did not control for medication exposures nor adjust for gestational diabetes.

2.2.2. Drugs, obstetrical complications in SLE and risk of congenital heart defects

Certain drugs used to treat SLE manifestations, such as methotrexate and mycophenolate mofetil, are known teratogens, and affected women might be inadvertently exposed to these agents during pregnancy, potentially increasing the risk of CHD.[87] In addition, it is well recognized that, in the conception period and the first trimester of pregnancy, maternal hyperglycemia can cause diabetic embryopathy resulting in major congenital anomalies.[92] The most frequent type of major congenital anomalies seen in women with pregestational and gestational diabetes is CHD.[92] Prior studies have shown that the likelihood of CHD in women with pregestational and gestational diabetes was respectively 3-fold and 1.5-fold increased risk relative to healthy women.[93,94] As women with SLE have an increased risk of gestational diabetes compared to the general population, this might result in an excess risk of CHD.

2.2.3. Prevalence of CHD in SLE offspring

Only very few uncontrolled observational studies have assessed CHD in offspring of mothers with SLE. Notably, in a study of fetal echocardiography in a small number of SLE pregnancies, 7.5% of fetuses had a CHD, which is more than 5-fold what is usually observed among live births from the general population (0.6-1.3%), although that is clearly not an equivalent comparison group.[95,96] A high prevalence of CHD has also been reported in 16-42% of children with congenital heart block born to anti-SSA/Ro-positive mothers, after excluding CHD that could have caused congenital heart block.[97-101] Although the prevalence of CHD was lower in children born to anti-SSA/Ro-positive mothers who did not develop congenital heart block (2.8%), the frequency was still substantially higher than in the general population.[100] In

such studies, the most frequently observed CHD were atrial septal defects, ventricular septal defects (VSD), and cardiac valve anomalies.[97-101]

2.2.4. Potential roles of maternal autoantibodies and cytokines in CHD

Maternal SLE-related mechanisms that could be implicated in the physiopathology of CHD in offspring, include autoantibody-mediated damage and cytokine imbalance. Transplacental transfer of maternal IgG antibodies begin in the second trimester, reaching circulating levels in the newborn that exceed maternal levels, due to active transport across the placenta.[102] Anti-SSA/Ro and anti-SSB/La antibodies, found in approximately 40% of women with SLE, cross the placenta and are associated with the development of neonatal lupus, with congenital heart block being the most characteristic cardiac manifestation.[103] Current data suggest that congenital heart block occurs in about 3% of pregnancies where these antibodies are present.[103] Investigators have demonstrated that maternal anti-SSA/Ro and anti-SSB/La antibodies bind fetal cardiocytes, resulting in the release of pro-inflammatory and pro-fibrosing cytokines, and ultimately scarring.[103] This process likely extends beyond the conduction tissue, involving the myocardium, endocardium. and valves. In a recent retrospective analysis of autopsies from 18 cardiac neonatal lupus cases, cardiac histological damage outside of the conduction system was frequently observed.[100] In particular, one autopsy showed a lympho-histiocytic infiltrate with inflammatory giant cells in the ventricular septum, while another displayed foci of microscopic calcification in the atrial septum. Moreover, 40% (6/15) of deaths due to congenital heart block had pathology findings such as fibrosis and calcification of the valves and/or valve apparatus, including the tricuspid, mitral, aortic and pulmonary valves.[100]

Cardiac septation occurs early in embryogenesis and is complete by 6 weeks of gestation.[104,105] Since transplacental passage of maternal autoantibodies only occur as early as the 20th week of gestation, it is unlikely that maternal autoantibodies directly interfere with cardiac septation.[102] However, muscular VSD, which account for approximately 75% of all VSD, are thought to arise from foci of cellular death that occur during active cardiac remodeling, within an already formed ventricular septum.[105] In addition, maternal autoantibodies might prevent closure of cardiac septal defects that might have closed otherwise, possibly explaining the excess risk of cardiac septal defects in offspring of SLE mothers compared to controls.

Antiphopholipid antibodies (aPL) are another type of autoantibodies commonly found in women with SLE, which also cross the placenta. In a recent study of children born to women with antiphospholipid syndrome, 40% of neonates had positive aPL in cord blood.[106] aPL are strongly associated with valvular disease (e.g. valvular nodules, regurgitation, and verrucous endocarditis) in aPL-positive adult patients with and without SLE.[107] Valvular deposits of aPL in affected adult subjects are thought to play an important pathogenic role in valvular disease.[107] Although prior studies have reported perinatal thrombotic events occurring in children born to aPL-positive mothers, there is currently no data on the prevalence of congenital valve anomalies or other types of CHD in these children.[108] Since aPL are involved in valvular damage in seropositive adult subjects and cross the placenta, it could be hypothesized that they may play a role in valve anomalies in exposed fetuses.

Cytokines, such as transforming growth factor beta (TGF-beta), play an important role in cardiac embryogenesis. In particular, adequate endocardial cushion formation, which is a critical step in cardiac septation, requires expression of TGF-beta.[109] The importance of both maternal and fetal TGF-beta in cardiac embryogenesis has been well illustrated in animal models.[109]

Notably, TGF-beta-1-null mice, born to TGF-beta-1-null mothers, demonstrate severe CHD, while TGF-beta-1-null mice born to wild-type mothers (i.e. with normal expression of TGF-beta-1) do not. Because transplacental transfer of circulating TGF-beta can occur from mother to fetus, investigators hypothesized that maternal TGF-beta-1 might rescue any potential heart defects in the null offspring.[109] Interestingly, in SLE patients, serum levels of TGF-beta-1 are substantially lower than in controls, with levels inversely correlating with disease activity.[110] Thus, maternal TGF-beta rescue of fetuses with defective TGF-beta levels might not occur in women with SLE, potentially accounting for the increased risk of CHD.

2.3. Neurodevelopmental disorders in offspring of mothers with SLE

2.3.1. Preamble to manuscript #2

In addition to having a potentially increased risk of CHD, some data suggest that children born to women with SLE may have a substantially increased risk of neurodevelopmental disorders compared to children born to healthy women. However, the evidence is extremely limited, as only a handful of small observational studies have assessed this issue. In manuscript #2, we review the current literature on neurodevelopmental disorders and their potential determinants in SLE offspring. This review article, entitled "Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus", was published in Lupus (2014; 23:1099-104). We provide a reprint of this article in Appendix F.

2.3.2. Title page

Title: Neurodevelopmental Disorders in Children Born to Mothers with Systemic Lupus Erythematosus

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2.3.3. Abstract

Children born to women with SLE seem to have a potentially increased risk of neurodevelopmental disorders compared to children born to healthy women. Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for neurodevelopmental disorders. Interestingly, women with SLE display high levels of autoantibodies and cytokines, which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring. Furthermore, subjects with SLE and neurodevelopmental disorders share a common genetic predisposition, which could impair the fetal immune response to in utero immunologic insults. Moreover, SLE pregnancies are at increased risk of adverse obstetrical outcomes and medication exposures, which have been implicated as potential risk factors for neurodevelopmental disorders. In this article, we review the current state of knowledge on neurodevelopmental disorders and their potential determinants in SLE offspring.

2.3.4. Introduction

In North America, the prevalence of neurodevelopmental disorders, such as autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD), has reached epidemic levels, affecting approximately 10% of school-age children.[111,112] Systemic lupus erythematosus (SLE) is a multi-systemic disease, which predominantly affects women during their childbearing years. Children born to women with SLE seem to have a potentially increased risk of neurodevelopmental disorders compared to children born to healthy women.[8-12,113] Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for neurodevelopmental disorders.[114] Interestingly, women with SLE display high levels of autoantibodies [e.g. anti-N-methyl-D-aspartate receptor (NMDAR) antibodies] and cytokines [e.g. interleukin-6 (IL-6)], which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring.[115,116] Furthermore, subjects with SLE and neurodevelopmental disorders share a common genetic predisposition to the C4B null allele, which could impair the fetal immune response to in utero immunologic insults.[117-119] Moreover, SLE pregnancies are at increased risk of adverse obstetrical outcomes, such as prematurity and low birth weight (LBW), and medication exposures, such as anticonvulsants, which have been implicated as potential risk factors for ASD and ADHD.[120-122] In this article, we review the current state of knowledge on neurodevelopmental disorders and their potential determinants in SLE offspring.

2.3.5. Overview of autism spectrum disorders and ADHD

ASD are now one of the most common neurodevelopmental disorders, with a prevalence ranging from 1/68 to 1/500 children.[112, 123] ASD are a group of biologically-based

neurodevelopmental disorders, characterized by onset before the age of 3 years, and impairment in three major domains: socialization, communication, and behavior.[123] ASD are diagnosed clinically and include: autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified.[123]

ADHD prevalence in school-age children is approximately 8-10% percent, making it one of the most common disorders of childhood.[111] ADHD is a neurodevelopmental disorder that manifests in early childhood with symptoms of hyperactivity, impulsivity, and/or inattention. ADHD symptoms affect cognitive, behavioral, emotional, and social functioning, and it is the persistence and functional complications of the behavioral symptoms that lead to a diagnosis of ADHD.[124] Notably, to meet criteria for ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders 4th Edition* (DSM-IV), symptoms must be present before the age of 7 years.[124]

Multiple inter-related factors potentially play an etiologic role in neurodevelopmental disorders. Increasing evidence supports a strong genetic contribution in the development of ASD and ADHD.[125] Neuroimaging and autopsy studies in neurodevelopmental disorders suggest that structural brain anomalies are implicated, such as prefrontal cortical volume disparities and hypofunction (present in both ASD and ADHD).[126,127] Though the literature shows conflicting results, perinatal factors including preterm birth, LBW, and in utero exposure to maternal smoking, as well as advanced parental age (both paternal and maternal) and maternal obesity have been associated with an increased risk of neurodevelopmental disorders in offspring.[120,121,123,124,128]

2.3.6. Neurodevelopmental disorders in offspring of mothers with SLE

Some epidemiological data suggest that children born to women with SLE may have an increased risk of neurodevelopmental disorders compared to children born to healthy women. However, the evidence is extremely limited, as only a handful of small observational studies have assessed this issue.

Several retrospective studies suggest that children, more particularly sons, of mothers with SLE are at increased risk (up to 25-45%) for learning disabilities, such as dyslexia.[9,11,112] In a small retrospective study using parental-report, the prevalence of learning problems due to inattention and hyperactivity in offspring of SLE mothers was more than twice that reported for controls.[112] Recently, a prospective study assessed the neurodevelopment of 57 children born to mothers with SLE and 49 controls using standardized tests.[8] Offspring of SLE mothers had more than a 3-fold increase in anomalies related to learning and memory, as well as behavior.

Moreover, autoantibodies commonly found in SLE patients have been associated with an increased risk of neurodevelopmental disorders.[129-131] Notably, in a small cohort study of children born to mothers with anti-Ro antibodies, investigators have shown that exposure to anti-Ro antibodies (present in 30-50% of SLE patients) is associated with a high parent-reported prevalence of ADHD, present in up to 24% (8/33) of exposed children.[129] In addition, in utero exposure to antiphospholipid (aPL) antibodies (found in up to 30% of subjects with SLE) has been linked to a high prevalence of learning disabilities (4/17 exposed children) and ASD (3/45 exposed children) in 2 small cohort studies of children born to aPL antibodies-positive mothers.[131,132] In a recent retrospective cohort study of 60 SLE offspring, in utero exposure to azathioprine conferred more than a 6-fold increased risk of having special educational needs

(used as a proxy for developmental delays), when adjusting for disease severity and obstetrical complications.[12]

Although previous studies support the hypothesis of an increased risk of neurodevelopmental disorders in offspring of SLE mothers, these studies were marked by important methodological limitations: all had limited sample size, only one controlled for obstetrical complications and medication exposures, and most used parental-report, did not include a control group, and/or were retrospective in nature.

2.3.7. Case-control studies of SLE in mothers of children with neurodevelopmental disorders

In addition to cohort evidence of an increased risk of neurodevelopmental disorders in offspring of mothers with SLE, numerous case-control studies have suggested an increased prevalence of SLE and other autoimmune diseases, in mothers of children affected with neurodevelopmental disorders.[133-135] In a case-control study of 61 children with ASD and 46 healthy controls, affected children had more than a 8-fold increase in the odds of having a mother with an autoimmune disorder (by her self-report) than unaffected children.[135] Among the most common maternal autoimmune disorders, SLE was observed in 13% of children with ASD, versus 4% of healthy controls.

A large population-based study using administrative data showed similar results, although the estimates were more conservative.[133] In this study, children with ASD were more likely than unaffected children to have a mother diagnosed with an autoimmune rheumatic disease such as SLE (RR 1.56, 95% CI 1.08, 2.17), while the likelihood of having a father with these diseases did not differ. This suggests that the association between SLE and

neurodevelopmental disorders might be influenced by a prenatal exposure to maternal antibodies and/or fetal environment during gestation.

2.3.8. Role of maternal antibodies in neurodevelopmental disorders

Currently, in utero exposure to maternal immunoglobulin G (IgG) antibodies is attracting great attention as an important environmental risk factor for neurodevelopmental disorders. It is well known that maternal IgG antibodies begin to cross the placenta at the second trimester of pregnancy, reaching circulating levels in the newborn that exceed maternal levels, due to active transport across the placenta.[114] In the presence of maternal autoimmunity, autoantibodies also cross the placenta and can interfere with fetal development. Although offending maternal autoantibodies are cleared from the child's circulation within the first 6 months of life, it is known that autoantibody-mediated injury in utero can result in long-term damage to organs (e.g. congenital heart block in neonatal lupus).[136]

Though the blood-brain barrier blocks IgG entry into the adult central nervous system (CNS), in the fetus, the immature blood-brain barrier allows IgG access to the developing brain.[114] Genetic predisposition may increase the susceptibility to neurodevelopmental disorders in children exposed in utero to offending maternal IgG.[137]

Antibodies directed against fetal brain proteins (proteins yet to be identified) have been observed in 10-12% of mothers of children with ASD.[114] This antibody reactivity has been shown to be *absent* in mothers of normally developing children. Also, human maternal fetal brain-reactive antibodies from mothers of children with ASD, when administered to pregnant mice, cause behavioral alterations in the offspring, including hyperactivity and decreased social interaction.[138] In this mouse model, an increased number of microglial cells were observed in

the brain of exposed offspring, suggesting that these brain-reactive antibodies may mediate their effects through inflammatory changes.[138]

Furthermore, studies have demonstrated a significant association between maternal fetal brain-reactive antibodies and specific patterns of ASD.[114] For example, children with ASD whose mothers harbored fetal brain–reactive antibodies were more likely to have a regressive form of autism than unexposed children.[139] In addition, Diamond et al. recently showed that 53% of mothers of an ASD child with fetal brain-reactive antibodies also exhibited anti-nuclear autoantibodies compared with 13% of ASD mothers without fetal brain-reactive antibodies and 15% of control women.[140] They also observed an increased prevalence of autoimmune diseases, especially SLE, in ASD mothers with fetal brain-reactive antibodies. These findings suggest that a subset of ASD might be related to in utero maternal antibody exposure, a mechanism potentially involved in cases born to SLE mothers.

2.3.9. Autoantibodies and cytokines in SLE potentially affecting fetal neurodevelopment

New experimental data have further substantiated a potential link between in utero exposure to SLE and neurodevelopmental disorders. A subset of anti-dsDNA antibodies, the anti-NMDAR antibodies, present in up to 60% of women with SLE, has been shown, in a mouse model, to cross the placenta, induce fetal brain neuronal apoptosis by binding NMDAR, and cause cognitive impairments in offspring, preferentially in males.[115,140) Affected offspring displayed smaller-sized neocortical neurons and neuronal migration defects, findings observed in histological studies of humans affected with learning disabilities and ADHD.[126]

It is noteworthy that pregnant mice exposed to anti-NMDAR antibodies had a marked preferential loss of female fetuses, resulting in an increased male-to-female ratio in their

offspring compared to the offspring of unexposed mice.[115] Interestingly, we have recently demonstrated that mothers with SLE had substantially increased odds of having male offspring than mothers without SLE (OR 1.18, 95% CI 1.01, 1.38) using our large population-based cohort.[141] This finding mirrors experimental data and parallel the male predominance seen in neurodevelopmental disorders.

Of particular interest, in human studies, mutations in genes leading to reduced NMDAR function have been associated with ASD and ADHD.[142-146] In addition, the NMDAR partial agonist d-cycloserine has been shown to restore NMDAR function and efficaciously treat the core symptom of social withdrawal in children with ASD.[147]

In addition to anti-NMDAR antibodies, other autoantibodies found in SLE could potentially alter fetal brain development. Antiphospholipid antibodies, present in 30% of women with SLE, are known to cross the placenta and have been found at high levels in the serum of exposed neonates.[130] These antibodies can bind CNS cells and, in experimental models, prolonged exposure to aPL antibodies induces hyperactive behavior and neurological dysfunction in mice.[148,149] Thus, these autoantibodies might also be implicated in inducing neurodevelopmental disorders in children born to women with SLE.

As well as maternal antibodies, maternal cytokines may reach the fetal circulation.[125] The maternal cytokine milieu might constitute an important environmental risk factor for neurodevelopmental disorders. Notably, interleukin-6 (IL-6) is known for its primordial role in brain development.[116] IL-6 administration in pregnant mice caused substantial behavioral and social deficits in the offspring, while co-administration with an anti-IL-6 antibody prevented these deficits.[116]

IL-6 is involved in autoantibody production in SLE, and affected patients have markedly elevated IL-6 blood levels.[19] Thus, in SLE pregnancies, IL-6 could possibly have a direct effect on the fetal brain or enhance the production of maternal fetal brain-reactive antibodies, which could cross-react with the fetal brain, leading to neurodevelopmental disorders in exposed fetuses.

2.3.10. Genes associated with SLE and neurodevelopmental disorders

Genes long implicated in autoimmune disorders, such as SLE, are significantly more prevalent in subjects with ASD and ADHD.[125] One of these genes is the C4B null allele, which is strongly associated with SLE. Depending on the population studied, SLE subjects are up to 6 times more likely than controls to harbor the C4B null allele.[117] Of particular interest, the C4B null allele is 4 times more common in individuals with ASD compared with controls.[118] Moreover, the C4B null allele has also been associated with ADHD, being present in 57% of affected subjects compared to 20% of controls.[150] As presence of the C4B null allele leads to partial C4B deficiency, and since the complement system is involved in brain tissue remodeling and repair, alterations in C4B levels could alter the fetal immune response to in utero immunologic insults, resulting in pathologic changes.[150]

2.3.11. Drugs, obstetrical complications in SLE and risk of neurodevelopmental disorders

SLE pregnancies are at increased risk of adverse obstetrical outcomes, such as prematurity and LBW, which are potential risk factors for ASD and ADHD. Approximately 25% of lupus pregnancies end in preterm birth and 15% of the neonates are LBW.[27,42] Observational studies report a 1.5-3-fold increase in neurodevelopmental disorders in children

born preterm or LBW vs controls.[151,152] Thus, obstetrical complications in women with SLE may also increase neurodevelopmental disorders in offspring.

In the general population, very few data exist on drug exposures during pregnancy and neurodevelopmental disorders in offspring. Anticonvulsant use during pregnancy, in particular valproic acid, has been associated with an increased risk of ASD in children from the general population.[122] Women with SLE are possibly more likely than unaffected women to be exposed (inadvertently or not) to certain drugs during pregnancy, including anticonvulsants (used to control SLE-related seizures or other neurological manifestations). Moreover, as potentially suggested in the study by Somers et al.,[12] in utero exposure to immunosuppressives, such as azathioprine, might mediate the risk of neurodevelopmental disorders in children of mothers with SLE. However, more studies are needed to confirm this potential drug effect, as it might also represent confounding by disease severity. In addition, uncontrolled disease activity as a consequence of drug avoidance during pregnancy might be associated with an even greater risk of neurodevelopmental disorders than in utero drug exposure itself.

To summarize, SLE is an important autoimmune disease and recent evidence suggests an increased risk of neurodevelopmental disorders in children born to affected women. The offspring of SLE mothers face several potential risk factors for neurodevelopmental disorders, including in utero exposure to maternal antibodies and cytokines, obstetrical complications, and drugs. In addition, both SLE and neurodevelopmental disorders share a common genetic predisposition. Thus, it is imperative to further study neurodevelopmental disorders and their determinants in the offspring of SLE mothers.

2.4. Literature review conclusion

Women with SLE face several disease-related factors that might lead to a reduced live birth rate, as well as an increased risk of CHD and autism spectrum disorders in their offspring compared to unaffected women. Therefore, this thesis work aimed to evaluate these important outcomes in women with SLE compared to women from the general population, as will be discussed next.

3. Research objectives

The objectives of this doctoral thesis were:

1) to determine if maternal SLE reduces the number of live births in affected women compared to women from the general population;

2) to evaluate if maternal SLE alters the long-term health of children born to affected mothers compared to children born to mothers without SLE. In particular, we aimed to assess if maternal SLE increases the risk of CHD and autism spectrum disorders in exposed offspring versus unexposed children.

4. Live births in women with SLE

4.1. Results from an international inception cohort

4.1.1. Preamble to manuscript #3

Until now, what has been reported in the literature is the proportion of pregnancies resulting in live births in women with SLE, not the live birth rate. The live birth rate is usually referred to as the fertility rate and defined as the number of live births per 1000 women of reproductive years (usually between 15-50 years) in a given year.[153] The live birth rate is thus influenced by two key reproductive outcomes: the number of pregnancies and the number of live births in a group of women. Furthermore, it is an important demographic statistic systematically recorded at a national and/or provincial level. Therefore, by using standardized incidence ratios (SIR), we would be able to directly compare the live birth rate in women with SLE to the live birth rate in the general population.[154] As the live birth rate in the general population varies with age, race, and calendar time, the SIR offers the advantage to allow direct comparison of women with SLE, at different ages (or stages of their reproductive period), from different races, and born at different periods, to the general population, providing a summarized measure. This measure would provide an answer as to whether SLE influences the number of children affected women have.[154] Therefore, in manuscript #3, we calculate the number of live births in a cohort of women diagnosed with SLE during their reproductive years, and compare this with general population rates, using SIR.[15] This study, entitled "Decreased live births in women with systemic lupus erythematosus", was published in Arthritis Care & Research (2011;63:1068-72). A reprint of the article is provided in Appendix F.

4.1.2. Title page

Title: Decreased Live Births in Women with Systemic Lupus Erythematosus

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4.1.3. Abstract

Purpose: Multiple disease-related factors may limit the number of children borne to women with SLE. We calculated live births in women with SLE, and compared this with general population rates.

Methods: We studied women with SLE from a subset of centers participating in the Systemic Lupus International Collaborating Clinics (SLICC) Prospective Inception Cohort Study of SLE. Women diagnosed with SLE before age 50 were included. Using age, calendar-period, and country-specific general population birth rates, we calculated the standardized incidence ratio (SIR) of observed to expected live births. We also performed a multivariate analysis with the SIR as the dependent variable to explore potential predictors of live births.

Results: 339 women with SLE were studied. The number of live births over the interval (313) was substantially below that which would be expected (479) (SIR 0.65; 95% CI 0.58-0.73). In multivariate analyses, black race/ethnicity (SIR 1.47; 95% CI 1.08-2.00) and being married or living common-law (SIR 2.04; 95% CI 1.52-2.74) were associated with increased live births (relative to what would be expected). There were trends for fewer live births in women exposed to cyclophosphamide (SIR 0.88; 95% CI 0.56-1.38) and in those with high disease activity (mean SLE Disease Activity Index-2K score ≥ 5) (SIR 0.82; 95% CI 0.54-1.25).

Conclusion: Overall, we found that women with SLE have fewer live births compared with the general population. Marital status, race/ethnicity, and possibly clinical factors may mediate this effect.

4.1.4. Introduction

Multiple disease-related factors may limit the number of children borne to women with systemic lupus erythematosus (SLE). These factors potentially include decreased fertility, adverse pregnancy outcomes (e.g., miscarriages or stillbirths), relative contraindications to pregnancy (e.g., high disease activity or dependence on a teratogenic medication), impaired sexual function and/or personal relationships, or a deliberate decision to limit family size.[13]

Many women with SLE ask if the disease will affect their capacity to have children, but studies assessing the impact of SLE on family size are scant. One case-control study suggested that white women with SLE appeared less likely to have more than 2 children compared with healthy controls, but the results were not precise (odds ratio [OR] 0.56; 95% confidence interval [95% CI] 0.31-1.03).[4] In a population-based study of women with rheumatic diseases, a lower number of births was observed in women with connective tissue diseases, including SLE, compared with controls (mean 1.7; 95% CI 1.5-1.9 versus 2.2; 95% CI 2.1-2.3).[5] The interpregnancy interval was longer and the proportion of women achieving a subsequent pregnancy was reduced in women with connective tissue diseases. Although these studies suggest a potential negative impact of SLE on family size, they are limited; both studies were small and only one specifically evaluated women with SLE. In addition, neither restricted the analysis to women diagnosed with SLE before or during their reproductive period, nor adjusted for the reproductive period duration.

Therefore, our primary objective was to calculate the number of live births in a cohort of women diagnosed with SLE during their reproductive years, and to compare this with general population rates. We also explored potential demographic, social, and clinical factors that might be associated with lower birth rates in women with SLE.

4.1.5. Subjects and Methods

We studied women with SLE from centers participating in the Systemic Lupus International Collaborating Clinics (SLICC) Prospective Inception Cohort Study of SLE and agreeing to share data for the present study. The SLICC inception cohort enrolls patients within 15 months of meeting ≥ 4 American College of Rheumatolgy (ACR) classification criteria for SLE. Demographic and clinical data, including number of children and age at first birth (although not dates of subsequent births), are prospectively collected using a standardized questionnaire.

We assessed the number of children born to women with SLE, evaluating only women diagnosed with SLE before the age of 50 years. We determined the number of children borne (both before and after SLE diagnosis) as of the last follow-up visit (the observed number of live births), in order to calculate the standardized incidence ratio (SIR). The SIR is the ratio of the observed number of live births in a sample divided by the expected number of live births. We determined the expected number of live births as follows. We summed the years of followup from the age of 15 years up to the age of 50 years (or the oldest age attained, if the subject was aged <49 years). We applied age- and country-specific general population birth rates, for the relevant calendar-periods, to these years of follow-up to obtain the expected number of births for the period of follow-up. Race-specific birth rates were only available for the United States (US). In sensitivity analyses, we applied these rates to the overall sample to adjust for its racial distribution.

In secondary analyses, we explored potential predictors of live births using multivariate Poisson regressions with the SIR (not itself adjusted for race/ethnicity) as the dependent variable. The potential predictors of live births included in the analyses were: race/ethnicity, marital status, age at diagnosis, disease duration, cyclophosphamide exposure (i.e. ever/never exposed),

presence of antiphospholipid antibodies (aPLa) (either lupus anticoagulant, anti-beta(2)-glycoprotein I, or anticardiolipin antibodies, on at least one occasion), disease activity (defined by the mean SLE Disease Activity Index-2000 [SLEDAI-2K] score) and damage (defined by the SLICC Damage Index [SDI] score). Time-dependent variables (including mean SLEDAI-2K and SDI scores) were assessed at the last follow-up.

As repeated reproductive outcomes are not independent, we applied the Huber-White correction to our multivariate model using all births and performed a sensitivity analysis restricted to first births, using parity-adjusted birth rates (that is, general population rates for first births, comparing live birth rates for first births in women with SLE to the general population), to assess the statistical validity of our multivariate model.

4.1.6. Results

339 women with SLE from 11 centers were studied. The mean age at diagnosis was 35.3 years (standard deviation [SD] 13.3) and the mean disease duration at the last visit was 2.7 years (SD 2.0). Most (43%) women were from the US, 27% from Canada, 27% from the United Kingdom, and 3% from Sweden. The majority (61%) was white and most (42%) were currently married or living common-law.

Regarding reproductive history, the mean age at menarche was 12.9 (SD 1.6) and the mean age at menopause was 45.5 (SD 7.9). The majority (54%) never had a live birth, with 42% reporting never having been pregnant. The mean age at first birth was 25.2 (SD 6.2) and almost all (89%) first births occurred before SLE diagnosis.

478 pregnancies were observed from age 15 years up to the subject's age at the last visit (Table 4.1.1.). Among 293 women for whom complete information on abortions was available,

74% of pregnancies resulted in live births, 20% in spontaneous abortions, and 6% in elective terminations.

Table 4.1.1. Reproductive events from age 15 years to end of followup

Table 1. Reproductive events from age 15 years to end of followup*

Events, no.	Gravidity (n = 339)	Parity (n = 339)	Spontaneous abortion (n = 293)	Therapeutic abortion (n = 293)
0	142 (41.9)	184 (54.3)	242 (82.6)	277 (94.5)
1	59 (17.4)	56 (16.5)	37 (12.6)	14 (4.8)
2	58 (17.1)	54 (15.9)	7 (2.4)	1 (0.3)
3	41 (12.1)	33 (9.7)	6 (2.1)	1 (0.3)
4	25 (7.4)	11 (3.2)	1 (0.3)	0 (0)
5	8 (2.4)	1 (0.3)	0 (0)	0 (0)
≥6	6 (1.8)	0 (0)	0 (0)	0 (0)

* Values are the number (percentage) unless otherwise indicated.

Overall, the number of live births over the interval (N=313) was substantially below that which would be expected (N=479) (SIR 0.65; 95% CI 0.58-0.73) (Table 4.1.2.). We found almost identical results using race-specific general population birth rates (SIR 0.65; 95% CI 0.58-0.72). The difference between the observed and the expected number of live births over the interval was attenuated when we restricted the analysis to first birth only (SIR 0.92; 95% CI 0.78-1.07).

Table 4.1.2. Live births in women with onset of systemic lupus erythematosus before age 50 years (n=339)

Table 2. Live births in women with onset of systemic lupus erythematosus before age 50 years (n = 339)*

	Observed, no.	Expected, no.	SIR	95% CI
All births†	313	479	0.65	0.58–0.73
First births‡	156	170	0.92	0.78–1.07

* SIR = standardized incidence ratio; 95% CI = 95% confidence interval.
† Expected live births calculated from age-, country-, and calendar-specific general population rates.
‡ Expected live births calculated from age-, country-, calendar-, and parity-specific general population rates.

Multivariate analyses (with SIR as the dependent variable) were performed with either all births, or first births only, yielding similar results (Table 4.1.3.). In these analyses, the SIR itself was not adjusted for racial differences in national birth rates, but we did include variables for race/ethnicity in our models. Black race/ethnicity (SIR 1.47; 95% CI 1.08-2.00) and being married or living common-law (SIR 2.04; 95% CI 1.52-2.74) were associated with increased live births (relative to what would be expected).

We observed fewer live births in Asian women (SIR 0.50; 95% CI 0.28-0.89). This represents a relative decrease in live births for Asian women diagnosed with SLE, versus the general population, in contrast to women with SLE of other ethnicities. In addition, there were trends for fewer live births in women exposed to cyclophosphamide (SIR 0.88; 95% CI 0.56-1.38) and in those with high disease activity (mean SLEDAI $\geq$ 5) (SIR 0.82; 95% CI 0.54-1.25).

We did not definitively establish a decrease in live births independently associated with the presence of aPLa (SIR 0.94; 95% CI 0.67-1.33) or disease damage (SDI score $\geq$ 2) (SIR 0.99; 95% CI 0.65-1.51), when demographic and clinical characteristics were adjusted for.

Table 4.1.3. Multivariate analysis exploring predictors of live births in women with systemic lupus erythematosus

Table 3. Multivariate analyses exploring predictors of live births in women with systemic lupus erythematosus*

	Multivariate model	
	With all births, SIR (95% CI)	**With first births, SIR (95% CI)**
Race/ethnicity		
White (n = 207)	Reference	Reference
Black (n = 65)	1.47 (1.08–2.00)	1.67 (1.08–2.57)
Asian (n = 33)	0.50 (0.28–0.89)	0.62 (0.29–1.31)
Other (n = 34)	1.13 (0.67–1.90)	1.43 (0.79–2.59)
Marital status		
Single (n = 197)	Reference	Reference
Married/common-law (n = 142)	2.04 (1.52–2.74)	2.02 (1.40–2.93)
Age at diagnosis, years		
<30 (n = 135)	Reference	Reference
≥30 (n = 204)	0.78 (0.56–1.08)	1.06 (0.70–1.64)
Disease duration, years		
<5 (n = 289)	Reference	Reference
≥5 (n = 50)	0.87 (0.63–1.21)	1.00 (0.64–1.57)
Cyclophosphamide exposure		
Never (n = 300)	Reference	Reference
Ever (n = 39)	0.88 (0.56–1.38)	1.04 (0.61–1.77)
Antiphospholipid antibodies		
No (n = 156)	Reference	Reference
Yes (n = 105)	0.94 (0.67–1.33)	1.06 (0.71–1.59)
Disease activity (mean SLEDAI-2K score)		
<1 (n = 71)	Reference	Reference
1 to <5 (n = 180)	0.92 (0.66–1.28)	0.95 (0.63–1.43)
≥5 (n = 88)	0.82 (0.54–1.25)	0.93 (0.55–1.56)
Disease damage (SLICC score)		
0 (n = 216)	Reference	Reference
1 (n = 43)	1.46 (1.05–2.01)	1.37 (0.88–2.15)
≥2 (n = 41)	0.99 (0.65–1.51)	1.00 (0.59–1.69)

* Standardized incidence ratio (SIR) is calculated using live births calculated from age-, country-, and calendar-specific general population rates, and is adjusted for country. 95% CI = 95% confidence interval; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 update; SLICC = Systemic Lupus International Collaborating Clinics.

4.1.7. Discussion

We observed that women diagnosed with SLE during their reproductive period have substantially decreased live birth rates compared to the general population. This finding persisted after adjusting for race/ethnicity, using race-specific birth rates. However, race/ethnicity was an important predictor of live births in the multivariate analysis, likely because the independent variable, SIR, was not itself adjusted for the varying of general population birth rates by race/ethnicity (that is, blacks in general have higher birth rates, and Asians lower than whites, even in the general population).

An additional important predictor of live births was marital status. The proportion of women in our sample (42%) who were either married or living common-law is somewhat lower than the different national rates of countries included in our study (48-58%).[155-157] This, and/or other issues related to personal relationships, may be factors contributing to our observed lower birth rate in women with SLE, compared to the general population.

In addition, early menopause could theoretically also contribute to low birth rates; the phenomenon of early menopause in SLE has been described by Cooper et al.[158] The mean age at menopause (45.5 years; 95% CI 30.0-61.0) in our sample was perhaps slightly lower than the general population average (51 years), although we did not have the precision to demonstrate statistical significance.[159] Of course, peak birth rate generally occurs well before menopause, although there is a steady increase, in the developed world, for birth rates in women above the age of 35.[160]

A limitation of our study is that we only had information on date of first birth, not dates of subsequent births. Therefore, we were unable to estimate a SIR for all live births specifically before and after SLE diagnosis. However, the SIR estimate which focused on first births (89% of

which occurred before SLE) showed no significant difference between observed and expected live births, suggesting that live births are not reduced before SLE diagnosis.

Moreover, as we only had information on date of first birth, we were unable to establish the timing of disease activity, aPLa status, and medication exposure respective to subsequent births. Therefore, we could not evaluate these covariates as time-varying and may explain why they were not strong predictors of live births.

Furthermore, although aPLa have been associated with recurrent pregnancy losses, it is still unclear if they are associated with infertility in humans.[161] A meta-analysis assessing the relationship of aPL antibodies with pregnancy rates and live birth rates following *in vitro* fertilization failed to show any negative association.[161]

We used information on parity from the SLICC inception cohort questionnaire; this does not actually differentiate between stillbirths and live births, so we may have misclassified stillbirths as live births. This may have over-estimated our live birth rate in women with SLE; hence, our results demonstrating lower live birth rates in women with SLE are likely conservative.

Several disease-related factors may contribute to reduced live birth rates in women with SLE. Although our study was not powered to assess these factors, since most of the births occurred prior to the SLE diagnosis, they warrant discussion. Women with no or mild disease activity in the 6 months preceding pregnancy are less likely to experience disease exacerbation.[3] For this reason, it is generally recommended that women have stable disease for 6 months before conceiving. In addition, certain drugs used to treat manifestations of active SLE, such as methotrexate and mycophenolate mofetil, are contraindicated during pregnancy because of potential fetal harm.[13] These medications must be discontinued or switched to safer ones in

prevision of conception. Dependence on a medication to maintain disease control or uncontrolled active disease may delay motherhood or increase the interval between pregnancies in some women.

Moreover, in women with SLE, fertility might be impaired due to associated autoimmune anomalies, therapies (e.g., cyclophosphamide), and hormonal dysfunction (e.g., transient amenorrhea).[13] Nevertheless, there is a general notion that SLE does not diminish fertility in affected women, although this aspect of reproduction has never been properly measured. Most authors cite a 1974 study by Fraga et al. that reported a fertility rate in women with SLE that was comparable with an age-matched control group of healthy women.[6] However, the fertility rate was calculated using the number of pregnancies in women who had at least 1 pregnancy. This largely overestimated the number of pregnancies per woman with SLE, as those who did not achieve any pregnancy were excluded.

Once pregnant, women with SLE are at increased risk of miscarriage and stillbirth. Approximately 20% of pregnancies in women with SLE will end in a miscarriage, compared with 9% in the general population.[4] We observed the same proportion of miscarriage in our SLE sample. Some studies have demonstrated that this risk was present even before SLE diagnosis, with almost a 2-fold increase compared with controls.[4,13] The risk of stillbirth has also been shown to be elevated in several studies, with an approximately 3-fold increase compared with general population statistics.[13] Obviously, miscarriages and stillbirths may directly contribute to a reduction in live births.

Women with SLE may also have impaired sexual function.[66] Physical problems (e.g., chronic pain) and emotional problems (e.g., depression) can decrease sexual interest and reduce intercourse frequency. Disturbances of hormonal status by corticosteroid treatment and disease

activity can reduce libido and interfere with successful reproduction.[66] Partnership difficulties arising from disease-related stress can also contribute to a less active sexual life.[66] In a study addressing this problem, 20% of SLE patients thought that their illness had driven their family apart or worsened their relationship with their partner.[68]

Faced with the potential risks of disease flare and/or adverse maternal and fetal outcomes, and considering the additional physical, social, and emotional demands related to the management of SLE, some women may choose not to have children. In a study assessing social functioning in 114 women with SLE, 27% viewed SLE as a barrier to childbearing.[7] Common concerns included worries that pregnancy might exacerbate the disease, that medications or the disease might harm the fetus, and that the disease might interfere with childcare.

In conclusion, compared with the general population, we found substantially decreased live birth rates in women with SLE, whose diagnosis occurred during reproductive years. Further study of the relative importance of demographic, social, and clinical factors will help confirm which sub-groups of women with SLE may be at greatest risk for decreased birth rates.

4.1.8. Supplementary material to manuscript #3

In the preceding manuscript, we evaluated live births in women with SLE. Reproductive outcomes, such as live births, are correlated (e.g. one woman with a previous adverse reproductive outcome is more likely to have a second one in the next pregnancy compared to another woman without an adverse pregnancy history). If we were to include all births in our analyses and ignore clustering, although our effect estimates would be valid, standard errors would be incorrect and might lead to inappropriate inferences.[162] Different approaches can be used to address correlation in birth outcomes. The simplest method consists in restricting the

analysis to the first identified birth per woman.[162] This subsample of births represents a well-defined population, providing results that are generalizable to the population of first births. In the case of estimating SIR of live births, we can apply parity-adjusted birth rate, allowing adjustment for the fact that live birth rates vary according to parity. However, there are two important drawbacks associated with the restriction to the first identified birth per woman.[162] First, there is a reduction in statistical power since we ignore available data, which results in larger standard errors than if we had included all data at hand. The second limitation is that results are only generalizable to the population of first births, i.e. they do not represent the experience of all births observed in the study population.

Therefore, an alternate approach would be preferable, such as one providing a correction of the standard errors, using all available data. As we mentioned previously, if we were to ignore clustering, we would consider that each individual observation provides information. However, in the presence of correlation between observations, the amount of information provided by each observation is less than if they were independant since knowing the value of one observation provides some degree of information on another one (from the same cluster).[162] Thus, the standard errors obtained through a standard regression analysis that does not account for correlation are smaller than they should be and must be corrected for the correlation to provide valid inference. To do so, we can use the Huber-White estimator which is a valid and non-parametric estimate of the standard error for a standard regression estimate.[162] The Huber-White correction estimates the true standard error by using the robust (also known as "empirical") covariance matrix of the data to adjust the standard errors obtained with the model assuming an independent correlation structure. Its main advantages are that it allows inclusion of all births in the analysis, providing more statistical power than when restricting the analysis to a

single birth outcome per woman. In addition, its validity is less sensitive to misspecification of the correlation structure than other approaches (for example random effect model, which will be discussed in Chapter 6.9), as it is a special form of generalized estimating equations (GEE), assuming an independent correlation structure.

Furthermore, to be valid, the Huber-White correction relies on the assumption that the missing data are missing completely at random (MCAR), i.e. observations are missing without the probability of missing being linked to any values in the dataset.[162] In our study, there were less than 5% of missing observations on covariates included in our regression models, which appeared to have been MCAR since covariate values for subjects with and without missing values were very similar. In addition, when missing values occur in less than 5% of observations, they are generally insufficient to cause substantial bias.[163]

In manuscript #3 (and as you will see in manuscript #4 as well) we used the two approaches described above, the Huber-White correction using all births and a restricted analysis to first birth only, to compare the effect estimates and the precision of the confidence intervals. Comparing the effect estimates allowed us to put in perspective the two "populations" studied, i.e. one representing all births and the other only first births, while comparing the width of the confidence intervals confirmed the statistical validity of our multivariate models.[162] As mentioned in manuscript #3, compared to the analysis including all births, the difference between the observed and the expected number of live births over the interval was attenuated when we restricted the analysis to first birth only [SIR with all births 0.65 (95% CI 0.58, 0.73) versus SIR restricted to first birth 0.92 (95% CI 0.78,1.07)]. As the SIR estimate which focused on first births showed no significant difference between observed and expected live births, and

since most first births (i.e. 89%) occurred before SLE diagnosis, this suggests that live births are not reduced before SLE diagnosis.

In Chapters 5 and 6, we will see two other approaches (i.e. GEE method and random effect models), which efficiently model the correlation structure of the observations and offer additional advantages for modeling clustered dataset.

4.2. Live births in women with SLE from a population-based cohort

4.2.1. Preamble to manuscript #4

As mentioned in manuscript #3, a limitation of our study is that we only had information on date of first birth, not dates of subsequent births. Thus, we were unable to estimate a SIR for all live births specifically before and after SLE diagnosis. However, as mentioned earlier, the SIR estimate which focused on first births (89% of which occurred before SLE diagnosis) showed no significant difference between observed and expected live births, leading us to hypothesize that live births in women with SLE are not reduced before diagnosis compared to the general population.[15]

To further investigate the impact of SLE diagnosis on live birth rates, i.e. to explore if live birth rates are particularly reduced after diagnosis, we performed a population-based study using Quebec's administrative databases.[16] Manuscript #4, entitled "A population-based assessment of live births in women with systemic lupus erythematosus," was published in Annals of Rheumatic Diseases (2012;71:557-9), and describes this study. A reprint of the article is provided in Appendix F.

4.2.2. Title page

Title: A Population-Based Assessment of Live Births in Women with Systemic Lupus Erythematosus

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4.2.3. Abstract

Objectives: To calculate the number of live births, both before and after SLE diagnosis, in women diagnosed with SLE during their reproductive years, and compare this with general population rates.

Methods: We identified women with SLE using Quebec administrative databases (1994/01/01-2003/12/31). We determined the number of live births, as defined by diagnostic and procedure codes for delivery, and calculated the standardized incidence ratio (SIR) of observed to expected live births.

Results: 1334 women with SLE were identified. Overall, the number of live births over the interval (559) was below that which would be expected (708) (SIR 0.79; 95%CI 0.73-0.86). Compared with the general population, live births were substantially lower after SLE diagnosis (SIR 0.62; 95%CI 0.55-0.70) than before diagnosis (SIR 1.01; 95%CI 0.90-1.13).

In multivariate analyses, prior hospitalization for SLE (RR 0.49; 95%CI 0.35-0.68) was associated with markedly decreased live births. There were trends for fewer live births in women with disease duration ≥5 years (RR 0.89; 95%CI 0.67-1.18) and in those living in rural regions (RR 0.83; 95%CI 0.61-1.13).

Conclusion: After diagnosis, women with SLE have substantially fewer live births compared with the general population. Prior hospitalization for SLE was the most important predictor of live birth in our sample.

4.2.4. Introduction

Upon being diagnosed with SLE, women of reproductive age often want to know if their disease will limit their ability to have children. Up to now, research has focused on a limited, although important aspect of this question: estimating the proportion of SLE pregnancies ending in live births. One further step in providing an adequate answer would be to assess live birth rates in women with SLE.

The live birth rate (also known as the fertility rate) is a useful demographic statistic and is defined as the number of live births per 1000 women of reproductive age (usually between 15-45 years) in a given year.[153] The live birth rate is thus influenced by 2 key reproductive outcomes: the number of pregnancies and the number of live births in a group of women**.** Multiple disease-related factors may limit live birth rates in women with SLE (see online supplementary text).[13]

The standardized incidence ratio (SIR), which is the ratio of the observed number of events in a sample divided by the expected number of events, allows us to directly compare the live birth rate in women with SLE to the live birth rate in the general population.[154] As the live birth rate in the general population is usually recorded according to age group and calendar time, the SIR offers direct comparison of women with SLE, at different reproductive stages, and born at different periods, to the general population by providing a summarized measure. Estimating such a measure should definitively answer whether having SLE influences the number of children affected women have.

Previously, we have performed a study determining the SIR of live births in women from an inception cohort of SLE,[15] using general population rates as a reference. We observed that women diagnosed with SLE during their reproductive period had substantially decreased live

birth rates compared to the general population (SIR 0.65; 95% CI 0.58-0.73). However, this study was limited in that we only had information on date of first birth, not dates of subsequent births. Thus, we were unable to estimate a SIR for live births specifically before and after SLE diagnosis.

To further investigate if live birth rates are reduced after SLE diagnosis, we performed a population-based study using administrative databases. Our primary objective was to calculate the number of live births, both before and after SLE diagnosis, in a cohort of women diagnosed with SLE during their reproductive years, and to compare this with general population rates using SIR.

4.2.5. Subjects and methods

We identified women with SLE using Quebec administrative databases (MED-ECHO and RAMQ physician billing databases, 1994/01/01-2003/12/31), which cover all healthcare beneficiaries. Incident SLE cases were women with ≥1 hospitalization with either a primary or secondary diagnosis of SLE, or ≥2 physicians' claims for SLE within any 2-month-to-2-year period, with no prior diagnosis of SLE in the 5 years preceding the interval. To assess women diagnosed with SLE during their reproductive period, only women aged 15-35 years on 1994/01/01 were included.

We determined the number of live births during the interval as defined by diagnostic and procedure codes for delivery in the MED-ECHO and RAMQ physician databases, respectively. As mentioned previously, the SIR is the ratio of the observed number of live births in a sample divided by the expected number of live births.[154] We determined the expected number of live births as follows. We summed the years of follow-up from the subject's age at the start of the

study interval up to the age of 45 years (or the oldest age attained at the end of the study period). For subjects who died during the interval, years of follow-up were summed up to the time of death. We applied age-specific general population birth rates, for the relevant calendar-periods, to these years of follow-up to obtain the expected number of births. We then calculated the SIR of observed to expected live births for the overall study interval, and both before and after SLE diagnosis.

We performed a multivariate Poisson regression to explore potential predictors of live births in women with SLE. Time-dependent predictors, assessed at the time of delivery, included prior hospitalization with a primary diagnosis of SLE, renal disease (i.e. RAMQ billing code for renal biopsy), antiphospholipid syndrome (i.e. ICD-9 code for antiphospholipid antibodies and/or any thrombo-embolic events in either databases), disease duration ≥5 years, and residence in rural regions (i.e. census <10 000 inhabitants). Because renal disease was defined using renal biopsy, which almost always requires a hospitalization, we included an interaction term between renal biopsy and hospitalization for SLE in the multivariate model.

We corrected our model for clustering of reproductive outcomes and performed a sensitivity analysis using first births (see online supplementary text).[162]

The McGill University Research Ethics Board approved this study.

4.2.6. Results

1334 women with SLE were identified (Table 4.2.1.). Overall, the number of live births over the interval (559) was below that which would be expected (708) (SIR 0.79; 95% CI 0.73-0.86)(Table 4.2.2.). Compared with the general population, live births were substantially lower

after SLE diagnosis (SIR 0.62; 95% CI 0.55-0.70) compared to before diagnosis (SIR 1.01; 95% CI 0.90-1.13).

Table 4.2.1. Patients' characteristics[a] (n=1334)

Characteristics	Women
Age at diagnosis, years (mean±SD)	28.9±8.0
Age at first birth, years (mean±SD)	28.6±5.1
Disease duration ≥5 years, n (%)	711 (53.3)
Living in a rural region, n (%)	288 (21.6)
Antiphospholipid syndrome, n (%)	321 (24.1)
Prior hospitalisation for SLE, n (%)	479 (35.9)
Renal disease, n (%)	148 (11.1)

Characteristics were determined at the end of the follow-up.
SLE, systemic lupus erythematosus.

Table 4.2.2. Live births (n=1334) in women with SLE diagnosis before 45 years

	Observed	Expected*	SIR	95% CI
Overall	559	708	0.79	0.73 to 0.86
Before SLE diagnosis	309	305	1.01	0.90 to 1.13
After SLE diagnosis	250	403	0.62	0.55 to 0.70

*Expected live births were calculated from age- and calendar-specific general population rates.
SIR, standardised incidence ratio; SLE, systemic lupus erythematosus.

In multivariate analyses of potential predictors of live births in women after SLE diagnosis (Table 4.2.3.), prior hospitalization for SLE (RR 0.49; 95% CI 0.35-0.68) was associated with markedly decreased live births. There were trends for fewer live births in women with disease duration ≥5 years (RR 0.89; 95% CI 0.67-1.18) and in those living in rural regions (RR 0.83; 95% CI 0.61-1.13).

Table 4.2.3. Multivariate analyses exploring predictors of live births in women with SLE (n=1334)

	Multivariate model with all births, RR (95% CI)	Multivariate model with first births, RR (95% CI)
Age at diagnosis		
Less than 30 years	Reference 1.10 (0.81 to 1.47)	Reference 1.13 (0.69 to 1.86)
30 years or more		
Disease duration		
Less than 5 years	Reference 0.89 (0.67 to 1.18)	Reference 0.91 (0.59 to 1.41)
5 years or more		
Living in a rural region		
No	Reference 0.83 (0.61 to 1.13)	Reference 0.68 (0.42 to 1.09)
Yes		
Antiphospholipid syndrome		
No	Reference 0.91 (0.65 to 1.29)	Reference 0.64 (0.36 to 1.12)
Yes		
Prior hospitalisation for SLE		
No	Reference 0.49 (0.35 to 0.68)	Reference 0.57 (0.33 to 0.96)
Yes		
Renal disease		
No	Reference 0.84 (0.34 to 2.04)	Reference 0.97 (0.24 to 3.98)
Yes		
Renal disease + prior hospitalisation for SLE		
No	Reference 1.95 (0.72 to 5.31)	Reference 1.93 (0.40 to 9.26)
Yes		

SLE, systemic lupus erythematosus.

We did not definitively observe a decrease in live births independently attributable to age at SLE diagnosis ≥30 years (RR 1.10: 95% CI 0.81-1.47), antiphospholipid syndrome (RR 0.91: 95% CI 0.65-1.29) or renal disease (RR 0.84; 95% CI 0.34-2.04). In addition, we did not establish any interaction between renal disease and prior hospitalization for SLE (RR 1.95; 95% CI 0.72-5.31). The multivariate analysis restricted to first births gave similar results, confirming the precision of our model for all births.

4.2.7. Discussion

We observed that women diagnosed with SLE during their reproductive period have substantially decreased live birth rates after diagnosis compared to the general population. We did not observe decreased live births in women with SLE prior to diagnosis. The most important predictor of decreased live births after SLE diagnosis was prior hospitalization for SLE, which likely indicates more severe/active disease.

We were unable to establish an independent association with renal disease, traditionally recognized as a marker of disease activity/severity, on live birth rates.[164] The definition we used for renal disease relied on renal biopsy, which often requires hospitalization. Since the primary discharge diagnosis in patients hospitalized to undergo a renal biopsy may have been SLE, the renal disease effect estimate may have been intermingled with the effect estimate for prior SLE hospitalization. To account for this possibility, our model did include an interaction term for renal disease and prior hospitalization, but failed to demonstrate an effect of renal disease, with or without a prior hospitalization, on live birth rates. Although our definition of renal disease aimed for high specificity, likely capturing patients with severe nephritis, it may have lacked sensitivity, potentially missing milder forms of nephritis. Only 11% of our SLE cohort was identified as having renal disease; this limited our power to find a small effect.

We were unable to demonstrate a decrease in live births due to antiphospholipid syndrome. No ICD-9 code exists for this syndrome and no claim-based definition has been validated. Thus, our definition, based on antiphospholipid antibodies and/or thrombo-embolic events, may have lacked specificity, biasing our effect estimate towards the null value due to non-differential misclassification.

We observed potentially decreased live births in women living in rural regions. This may be explained by limited healthcare accessibility, resulting in adverse pregnancy outcomes, deliberate decision to avoid pregnancy, and/or inappropriate counseling on pregnancy. Moreover, this difference may reflect variations in racial distribution between Quebec urban and rural regions, the latter being predominantly populated by Caucasians.[165] Since Caucasians are known to have one of the lowest live birth rates,[166] and since our multivariate analysis did not account for race, as this variable was not present in the database, this may explain reduced RR for live births in women from rural regions. However, it is unlikely that failure to adjust for race would explain our primary results, the SIR for live births both before and after diagnosis. Indeed, in our previous study,[15] decreased live birth rates in women with SLE (compared to the general population) persisted after applying race-specific birth rates. Furthermore, non-Caucasian groups such as blacks and Hispanics, who have increased live birth rates compared to Caucasians,[166] are generally over-represented in North American SLE cohorts (due to their higher rate of SLE).[167,168] Thus, if anything, our results are likely conservative (see online supplementary text for further discussion of limitations).

In conclusion, our findings indicate that live birth rates are substantially reduced (compared to the general population) after diagnosis in women with SLE, and that disease-related factors, such as prior hospitalization for SLE, potentially play an important role. These results prompt future research to further characterize disease-related, demographic, and psychosocial factors contributing to decreased live birth rates in women with SLE.

4.2.8. Appendix

4.2.8.a. Introduction

Multiple disease-related factors may limit live birth rates in women with SLE, either by affecting pregnancies and/or live births.[13] These include decreased fertility (due to associated autoimmune anomalies, therapies, and/or hormonal dysfunction), adverse pregnancy outcomes (e.g., miscarriages or stillbirths), relative contraindications to pregnancy (e.g., high disease activity or dependence on a teratogenic medication), impaired sexual function and/or personal relationships, or a deliberate decision to limit family size.[13]

4.2.8.b. Methods

Repeated reproductive outcomes are not independent since women with a past adverse obstetrical outcome have a higher probability to face this event in a subsequent pregnancy.[162] Thus, clustering must be accounted for in analyses of reproductive outcomes. Hence, we applied the Huber-White correction for clustering to our model using all births, and performed a sensitivity analysis restricted to first births, using parity-adjusted birth rates to assess the precision of our model.[162]

4.2.8.c. Discussion

Our SLE case definition has high specificity and good sensitivity. We have previously conducted a study using the same case definition (i.e. ≥1 hospitalization with either a primary or secondary diagnosis of SLE, or ≥2 physicians' claims for SLE within any 2-month-to-2-year period, with no prior diagnosis of SLE in the 5 years preceding the interval) within the same databases (i.e. MED-ECHO and RAMQ physician billing databases).[169] Using a Bayesian latent class model, we found high specificity (0.999) for SLE diagnosis, either using hospitalization or physician billing data, ensuring that cases labeled as SLE truly have the disease.

A previous validation study of administrative claims estimated the sensitivity of rheumatologist billing claims for SLE diagnosis to be 85%.[170] In other work by our group on the accuracy of systemic autoimmune rheumatic diagnoses from administrative data (versus medical charts), diagnoses were confirmed 81% of the time (680 of the 824 subjects), and in almost every instance when a specific diagnosis from administrative data was not confirmed by chart review, the subjects in fact had a related systemic autoimmune rheumatic disease (e.g. undifferentiated connective tissue disease, instead of SLE).[171]

A potential limitation of our study is variation in medical management over and since the observation period. Indeed, changes over time are important to consider in terms of relevance of the results to current practice. Our observation period actually covers a relatively short time interval in rheumatology (i.e. 10 years), up to 2003. Advancements in lupus treatment have been relatively slow; for example, antiphospholipid syndrome management did not drastically change since the mid 90s,[172] and although mycophenolate mofetil was first established for the treatment of lupus nephritis within the time of our study interval, many women with lupus nephritis are still being treated with drugs like cyclophosphamide and azathioprine. Thus, our results should be of considerable interest for physicians who currently treat SLE patients.

Unfortunately, we were unable to investigate the independent effect of medications, such as methotrexate and cyclophosphamide, on live births. The RAMQ database contains information on drug exposure only for individuals on the RAMQ prescription plan. The RAMQ prescription plan covers individuals 65 years and older, recipients of social assistance, and workers and their families who do not have access to a private drug insurance program. This includes approximately 36% of women between 15-45 years of age.[173]

In addition, based on a previous study done by our group, only 7% and 1% of Canadian women with SLE were respectively on methotrexate and cyclophosphamide.[174] Many more women were on antimalarials (66%) and azathioprine (17%), which are not contraindicated during pregnancy and have not been clearly associated with adverse pregnancy outcomes in this population. Thus, drug information limited to a subgroup of subjects and rare drug exposure pose power issues to assess the independent effect of medication.

Furthermore, in our previous study assessing live births in a SLE inception cohort, we did assess the effect of being ever exposed to cyclophosphamide.[15] We failed to demonstrate an effect; however, our effect estimate was imprecise as only a small number of our sample had been ever exposed to this agent. To further investigate the effect of medication on live births in SLE, we are currently planning a pan-Canadian population-based study.

It is likely that other chronic autoimmune diseases negatively impact live birth rates in affected women of reproductive age, albeit not as much as in SLE. We have recently done a study in women with systemic sclerosis (SSc), using a methodology similar to the present study.[175] Although we found that live birth rates were reduced after SSc symptoms onset compared to the general population (SIR 0.79, 95% CI 0.65-0.95), the effect seemed to be less profound than after SLE diagnosis. Other investigators have found reduced birth rates in women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis compared to a matched sample of unaffected women (respectively RR 0.88, 95% CI 0.84-0.93, and RR 0.84, 95% CI 0.77-0.92), but not to the extent that we documented in women with SLE.[176] This observation is not surprising and is consistent with the fact that women with SLE have more complicated pregnancies than women with other autoimmune rheumatic diseases. However, this observation needs to be confirmed in a single study, which we are currently conducting and which will

compare live birth rates after diagnosis in women respectively affected with SLE, RA, and SSc. Meanwhile, it is important to stress that our research is the first to estimate the effect of SLE on live birth rates after diagnosis. It is a necessary first step, which will prompt research to further characterize the disease-related predictors. Finally, it is crucial to quantify the differential effect of specific diseases, such as SLE, on live birth rates, because clinicians want to target the most affected groups and patients wish to know how their disease might limit their ability to have children.

4.2.9. Supplemental material for manuscript #4

As described in manuscripts #3 and #4, we have conducted two studies estimating live birth rates in women with SLE using SIR with general population rates as a reference. Both studies had very different study populations: one relied on an international inception cohort of women with SLE, the other on an SLE cohort derived from an administrative database.[15,16] This allowed us to investigate different predictors of live birth rates in women with SLE. Further studies are needed to clarify the relative importance of factors affecting live birth rates in women with SLE. Our study suggests that living in a rural region might potentially have a negative impact on live birth rates in women with SLE.[16] Investigating the influence of access to and/or quality of care on live birth rates might provide targets for potential interventions to allow women with SLE wishing to conceive to have a successful pregnancy.

Moreover, as discussed in Chapter 2.1.4., live birth rates in women with SLE might be influenced by childbearing decisions related to concerns about the disease. Notably, in a recent study by Clowse et al. assessing the reproductive experience of SLE women, those expressing concerns that their disease or medications would harm their baby had fewer conceptions than

women who did not indicate these concerns.[177] When caring for women with SLE contemplating pregnancy, it is difficult to appropriately address these concerns as little is known about the long-term outcomes of children born to women with SLE. It is imperative to fill this knowledge gap to improve pregnancy counseling in SLE women. The next two chapters will describe two studies assessing long-term outcomes in SLE offspring.

5. Congenital heart defects in offspring of SLE mothers

5.1. Preamble to manuscript #5

Congenital anomalies often have long-term health implications in affected offspring. An important aspect of pregnancy counseling relates to discussion of the risk of congenital anomalies associated with maternal illnesses and therapeutic interventions. However, little is known about the risk of congenital anomalies in SLE. In manuscript #5, entitled "Increased congenital heart defects in children born to women with systemic lupus erythematosus: results from the Offspring of Systemic Lupus Erythematosus Mothers Registry Study" and published in Circulation (2015;131:149-56)., we evaluate the risk of CHD in SLE offspring.[17] We provide a reprint of the article in Appendix F.

5.2. Title page

Title: Increased Congenital Heart Defects in Children Born to Women with Systemic Lupus Erythematosus: Results from the Offspring of Systemic Lupus Erythematosus Mothers Registry Study

Vinet: Congenital heart defects in SLE offspring

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5.3. Abstract

Background: In a large population-based study, we aimed to determine whether children born to women with systemic lupus erythematosus (SLE) have an increased risk of congenital heart defects (CHD) compared to children born to women without SLE.

Methods and Results: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's healthcare databases (1989-2009), and a randomly selected control group of women, matched ≥4:1 for age and year of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained CHD based on ≥1 hospitalization or physician visit with relevant diagnostic codes, within the first 12 months of life. We performed multivariable logistic regression analyses, using the generalized estimating equation method, to adjust for relevant covariates.

Five hundred and nine women with SLE had 719 children, while 5824 matched controls had 8493 children. Compared to controls, children born to women with SLE experienced more CHD [5.2% (95% CI 3.7-7.1) versus 1.9% (95% CI 1.6-2.2), difference 3.3% (95% CI 1.9-5.2)]. In multivariable analyses, children born to women with SLE had a substantially increased risk of CHD (OR 2.62, 95% CI 1.77-3.88) compared to controls. In addition, compared to controls, offspring of SLE mothers had a substantially increased risk of having a CHD repair procedure (OR 5.82, 95% CI 1.77-19.09).

Conclusions: Compared to children from the general population, children born to women with SLE have an increased risk of CHD, as well as an increased risk of having a CHD repair procedure.

5.4. Introduction

Systemic lupus erythematosus (SLE) predominantly occurs in women of childbearing age, with prevalence estimates of about 1.5/1000 in females aged 18-44 years.[2] This disease can cause considerable morbidity during pregnancy. Pregnant women with SLE and those contemplating pregnancy often ask if their disease will affect their baby. Although several studies have evaluated obstetrical outcomes in lupus pregnancy, little is known about the risk of congenital anomalies.

Congenital heart defects (CHD) are the most frequent type of birth defects, accounting for approximately a third of all congenital anomalies;[88] they are associated with substantial child morbidity.[89] In utero exposures, such as maternal illnesses and medications, are thought to play an important role in the yet to be fully elucidated etiology of CHD.[90] In particular, a recent study suggests a 3-fold increased risk of CHD in children born to mothers with various systemic connective tissue disorders, including SLE.[91] However, the investigators did not specifically assess the SLE effect estimate for the risk of CHD and did not control for medication exposures. Certain drugs used to treat SLE manifestations, such as methotrexate and mycophenolate mofetil, are known teratogens, and affected women might be inadvertently exposed to these agents during pregnancy, potentially increasing the risk of CHD.[87]

Only very few uncontrolled observational studies have assessed CHD in offspring of mothers with SLE. Notably, in a study of fetal echocardiography in a small number of SLE pregnancies,[95] 7.5% of fetuses had a CHD, which is more than 5-fold what is usually observed among live births from the general population (0.6-1.3%), although that is clearly not an equivalent comparison group.[96] Investigators have also observed CHD in 16-42% of children with congenital heart block born to mothers with anti-Ro/SSA antibodies, after excluding cases

with CHD that could have caused congenital heart block.[97-101] Although the prevalence of CHD was lower in children born to mothers with anti-Ro/SSA antibodies who did not develop congenital heart block (2.8%), the frequency was still substantially higher than in the general population.[97] In such studies, the most frequently observed CHD were atrial septal defects (ASD), ventricular septal defects (VSD), and valve anomalies.[97-101]

Given the paucity of existing literature, we aimed, in a large population-based study, to determine whether children born to women with SLE have an increased risk of CHD compared to children born to women without SLE. In addition, we aimed to determine if offspring of SLE mothers have an increased risk of particular CHD subtypes, including ASD, VSD, and valve anomalies, compared to offspring born to unaffected mothers.

5.5. Methods

5.5.1. Study design and subjects

The "Offspring of SLE mothers Registry (OSLER)" is a population-based cohort of 719 children born to mothers with SLE, matched to 8493 control children. To create this large cohort, we identified all women with SLE who had ≥1 hospitalization for a delivery resulting in a stillbirth or live birth, between January 1989 and December 2009, using data from the Quebec MED-ECHO ("Maintenance et Exploitation des Données pour l'Étude de la Clientèle HOspitalière") hospitalization and "Régie de l'Assurance Maladie du Québec (RAMQ)" physician billing databases.

MED-ECHO is the administrative database collecting information on all hospitalizations in Quebec since 1987, and provides, for each hospitalization, a primary discharge diagnosis and up to 15 non-primary diagnoses, captured as International Classification of Diseases (ICD)-9

codes, and since 2006, ICD-10 codes. RAMQ billing database records one physician-assigned diagnosis, based on ICD-9 codes, for each physician encounter.

5.5.2. Exposure of interest

Women were identified as SLE cases, based on a validated definition,[169] using 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. From these databases, a general population control group was composed of women individually-matched ≥4:1 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, which is present in every child's file in the RAMQ and MED-ECHO databases, and where it remains through childhood, leading to very few linkage failures (< 2%). Those children born live were the basis of the OSLER cohort for outcome ascertainment, one being the exposed group consisting of children born to women with SLE, and the other being the control group consisting of children born to women without SLE. Stillbirths were not included since a substantial proportion of births labeled as stillbirths in Quebec result from pregnancy termination, for which no information for our outcome of interest is recorded neither for SLE mothers, nor controls (see Online Data Supplements).[178]

5.5.3. Outcome assessment

The cohort of children described above was linked to the MED-ECHO and RAMQ databases to determine hospitalizations and all diagnoses occurring throughout the study interval of these offspring. This study interval spanned from birth to the first of the following: end of eligibility for RAMQ coverage (i.e. migration from Quebec), event of interest (e.g. CHD), age 1, death, or end of study (i.e. December 31st 2009).

Our ascertainment of CHD in live-born babies was based on the presence, at birth or within the first 12 months of life, of ≥1 ICD-9 code 745, 746, and 7471-7474 and/or ICD-10 code Q20-26, using the methodology developed by the "European Surveillance of Congenital Anomalies (EUROCAT)" network.[179] Use of ICD-9/10 codes for identification of CHD has been previously validated in Quebec's administrative databases.[180] We further excluded subjects with ICD-9/10 codes referring to congenital heart block and/or patent ductus arteriosus, as the only CHD. However, subjects with a diagnosis of congenital heart block and/or patent ductus arteriosus and any other CHD were included as cases. ASD, VSD, and valve anomalies were defined based on ≥1 relevant diagnostic code (see Online Data Supplement). We included records of CHD diagnosed within the first 12 months of life, to capture events with delayed detection or registration.

5.5.4. Assessing relevant covariates

For all mothers in our study, we reviewed the MED-ECHO and RAMQ data to identify specific pre-existing and current co-morbidities (i.e. hypertension, pregestational diabetes, asthma) recorded in the two years prior to the time of delivery, as well as obstetrical complications, such as gestational diabetes, at the time of the hospitalization for delivery. The diagnosis of specific co-morbidities listed above was based on ICD-9/10 codes indicating ≥1 hospitalization or ≥2

physician visits, at least 8 weeks apart, for the diagnosis of interest, as per previously validated methodology.[181,182]

Available through the "Institut de la Statistique du Québec" were data on the demographics of the parents at the time of delivery, including maternal education, as well as maternal and paternal birthplace, maternal language, and language spoken at home, which were used to establish the race/ethnicity of the offspring (see Online Data Supplement). These demographic data were used in our analyses as covariates.

Comprehensive and valid data on drug exposures is available from the RAMQ prescription (RAMQ-Rx) database, but only for beneficiaries of the public drug plan.[183] The RAMQ-Rx plan covers recipients of social assistance, and workers and their families who do not have access to private drug insurance. In our cohort, 22% of exposed children and 21% of controls were born to a mother with RAMQ-Rx plan coverage throughout pregnancy.

In this subgroup, we obtained all information on the prescription of certain types of medications, including corticosteroids, antimalarials, immunosuppressives, antidepressants, and anticonvulsants. Of note, there is no information recorded on intravenous cyclophosphamide exposure in the RAMQ-Rx database, as this medication is administered in hospital. We used gestational age recorded at birth to calculate back to the estimated start of the gestational period, then determined whether a medication exposure of interest ever occurred during pregnancy based on ≥1 prescription filled at any time during gestation.

5.5.5. Statistical analyses

We calculated the prevalence and computed the odds ratios (OR) for all types and specific subtypes of CHD in the group of children born to mothers with SLE versus the control group,

performing both univariable and multivariable regression analyses estimated with generalized estimating equations.[184] Missing data on education and race/ethnicity covariates, occurring in <6% of subjects, were handled by using multiple imputation (see Online Data Supplement).

In these analyses, we matched SLE exposed and unexposed children for maternal age group and calendar year of delivery, but we also further adjusted for maternal age and calendar year to control for potential confounding by these variables (see Online Data Supplement). In addition, we adjusted for relevant demographic factors and maternal co-morbidities, including the following: sex of child, birth order, maternal education, race/ethnicity, pregestational and gestational diabetes, maternal hypertension, and asthma. In the subsample with RAMQ-Rx plan coverage, we also adjusted for in utero maternal medication exposures, including oral corticosteroids, antimalarials (i.e. hydroxychloroquine or chloroquine), immunosuppressives (i.e. azathioprine, mycophenolate mofetil, mycophenolate sodium, and methotrexate), and any types of antidepressants. Of note, we excluded exposure to anticonvulsants from the subsample multivariable model because no CHD case was recorded for this covariate.

Moreover, we performed a sensitivity analysis to account for the possibility of detection bias. Indeed, offspring of SLE mothers are more likely to undergo fetal echocardiography as part of routine screening to detect congenital heart block in those exposed in utero to maternal anti-SSA/Ro and/or anti-SSB/La antibodies, which are present in up to 40% of women with SLE.[185] Hence, CHD might be more easily detected in children born to women with SLE than in controls, leading to an overestimation of the association. Thus, to account for this possibility, we re-ran the analysis excluding children who had ≥1 fetal echocardiography.

In addition, to investigate the clinical impact of a potentially increased risk of CHD in SLE offspring versus controls, we further assessed the risk of CHD repair procedures (see Online

Data Supplement), adjusting for the potential confounders mentioned above, except medication, due to the small number of procedure events in the subsample with public drug coverage.

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. The first author takes full responsibility for the accuracy and completeness of the data.

5.6. Results

Five hundred and nine women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age in the overall sample of mothers and mean SLE disease duration were respectively 30.3 (standard deviation, SD, 5.0) and 3.7 (SD 4.0) years (Table 5.1). Mothers with SLE had similar demographic characteristics compared to control mothers, except for race/ethnicity since they were less likely to be Caucasians (as expected, because black and Asian race/ethnicity may predispose to SLE).[2] In addition, mothers with SLE had more co-morbidities and experienced substantially more obstetrical complications, such as preterm births and pre-eclampsia/eclampsia, compared to control mothers. In utero drug exposures were more frequent in SLE offspring compared to controls, with exposures to corticosteroids and antimalarials being the most common drugs prescribed during SLE pregnancies. Among the 11 children with in utero immunosupressive exposures, all were exposed to azathioprine, with 7/11 having ≥3 records of the drug dispensed, and one child was additionally exposed to mycophenolate mofetil, albeit with only one record of the drug dispensed early in gestation.

Table 5.1. Characteristics of the SLE offspring and control children (n=9212) in Quebec's administrative databases, Canada, 1989-2009

Characteristics	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
Maternal characteristics			
Mean age, y (SD)	30.2 (5.1)	30.3 (5.0)	0.56
Mean education, y (SD)	14.0 (3.1)	13.8 (3.1)	0.07
Marital status, n (%)			
Couple	576 (80.1)	6904 (81.3)	0.65
Single	50 (7.0)	523 (6.2)	
Unknown	93 (12.9)	1066 (12.6)	
Comorbidities, n (%)			
Hypertension	47 (6.5)	87 (1.0)	<0.0001
Asthma	38 (5.3)	240 (2.8)	0.0002
Diabetes mellitus	23 (3.2)	143 (1.7)	0.003
Depression	11 (1.5)	38 (0.4)	0.0001
Paternal characteristics			
Mean age, y (SD)	33.2 (5.8)	33.3 (5.9)	0.47
Demographic characteristics			
Male sex, n (%)	402 (55.9)	4377 (51.5)	0.02
Ethnicity, n (%)			
White	444 (61.8)	6226 (73.3)	<0.0001
Other	275 (38.2)	2268 (26.7)	
Obstetric characteristics			
Mean gestational age, wk (SD)	37.7 (2.9)	38.8 (1.9)	<0.0001
Mean birth weight, g (SD)	2976 (707)	3367 (566)	<0.0001
Birth order, n (%)			
1	308 (42.8)	2333 (27.5)	<0.0001
≥2	411 (57.2)	6160 (72.5)	
Obstetric complications, n (%)			
Preterm birth	157 (22,0)	614 (7.3)	<0.0001
Small for gestational age	120 (16.7)	694 (8.2)	<0.0001
Gestational diabetes mellitus	30 (4.2)	263 (3.1)	0.11
In utero medication information			
Public drug coverage, n (%)	155 (21.6)	1770 (20.8)	0.65
Corticosteroids	34 (21.9)*	12 (0.7)†	<0.0001
Antimalarials	25 (16.1)*	1 (0.1)†	<0.0001
Immunosuppressives	11 (7.1)*	0 (0.0)†	<0.0001
Antidepressants	11 (7.1)*	52 (2.9)†	0.005
Anticonvulsants	1 (0.6)*	7 (0.4)†	0.49

SD indicates standard deviation; and SLE, systemic lupus erythematosus.

*Denominator used for proportion is number of children born to SLE mothers with public drug coverage during pregnancy.

†Denominator used for proportion is number of children born to control mothers with public drug coverage during pregnancy.

Compared to controls, children born to women with SLE experienced more CHD [5.1% (95% CI 3.7, 7.1) versus 1.9% (95% CI 1.6, 2.2), difference 3.2% (95% CI 1.9-5.2)], including more ASD, VSD, and valve anomalies (Table 5.2). In offspring with maternal drug coverage throughout pregnancy (n=1925), we observed 5 cases of CHD (4 born to SLE mothers and 1 to a control mother) among the 46 children exposed to corticosteroids, and one case of CHD in the 11 children exposed to immunosuppressives, all born to SLE mothers.

Table 5.2. Frequency of congenital heart defects and subtypes in SLE offspring and control children (n=9212) in Quebec's administrative databases, Canada, 1989-2000

Types	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
Any CHDs	37 (5.1)	159 (1.9)	<0.0001
Cardiac septal defects, n (%)	29 (4.0)	109 (1.3)	<0.0001
ASDs	21 (2.9)	68 (0.8)	<0.0001
Isolated* ASD	11 (1.5)	39 (0.5)	0.001
VSDs	12 (1.7)	56 (0.7)	0.002
Isolated VSD	6 (0.8)	38 (0.5)	0.15
Cardiac valve anomalies	7 (1.0)	26 (0.3)	0.009
Isolated valve anomalies	3 (0.4)	13 (0.2)	0.12
Other CHDs			
Other CHDs without ASD, VSD, and valve anomalies†	14 (1.9) 4 (0.6)	54 (0.6) 33 (0.4)	0.0006 0.53
CHDs with ≥1 extracardiac major congenital anomalies	5 (0.7)	15 (0.2)	0.02

Values are presented as n (%). ASD indicates atrial septal defect; CHD, congenital heart defect; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

*Isolated is defined as a specific subtype of CHD occurring without any other subtype of CHD.

†Among cases with other CHDs, but without ASD, VSD, and valve anomalies, the most frequent diagnosis in SLE offspring cases was pulmonary artery anomaly (2/4), whereas, in control cases, it was CHD not otherwise specified (12/34).

In multivariable analyses including all children (n=9212), children born to women with SLE had a substantially increased risk of CHD (OR 2.62, 95% CI 1.77-3.88) compared to controls (Table 5.3). Specifically, offspring of SLE mothers had substantially increased odds of ASD (OR 3.32, 95% CI 1.97-5.77), VSD (OR 2.50, 95% CI 1.31-4.75), and valve anomalies (OR 2.95, 95% CI 1.23-7.07) compared to controls. Other predictors of CHD included pregestational diabetes and asthma (Table 3).

Table 5.3. Multivariable analyses of the risk of all types of congenital heart defects and subtypes in the overall sample of children (n=9212) from Quebec's administrative databases, Canada, 1989-2009

Covariates	Any CHD OR (95% CI)	ASD OR (95% CI)	VSD OR (95% CI)	Valve Anomalies OR (95% CI)
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	2.62 (1.77–3.88)	3.32 (1.97–5.57)	2.50 (1.31–4.75)	2.95 (1.23–7.07)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.06 (0.79–1.42)	1.00 (0.66–1.53)	1.30 (0.80–2.11)	0.71 (0.35–1.44)
Education				
≤ High school	Reference	Reference	Reference	Reference
≥ College	0.94 (0.68–1.30)	0.87 (0.55–1.38)	1.16 (0.68–1.98)	1.01 (0.47–2.20)
Ethnicity				
White	Reference	Reference	Reference	Reference
Other	1.28 (0.90–1.81)	1.35 (0.84–2.19)	1.47 (0.85–2.55)	1.30 (0.57–2.94)
Pregestational diabetes mellitus				
No	Reference	Reference	Reference	Reference
Yes	2.05 (0.99–4.23)	2.54 (1.03–6.27)	3.56 (1.24–10.17)	2.14 (0.46–10.02)
Gestational diabetes mellitus				
No	Reference	Reference	Reference	Reference
Yes	1.17 (0.54–2.54)	1.01 (0.31–3.26)	3.05 (1.28–7.25)	2.07 (0.48–8.96)
Hypertension				
No	Reference	Reference	Reference	Reference
Yes	1.59 (0.70–3.64)	2.04 (0.76–5.53)	0.56 (0.07–4.24)	0.91 (0.11–7.66)
Asthma				
No	Reference	Reference	Reference	Reference
Yes	2.76 (1.63–4.71)	2.00 (0.89–4.53)	1.24 (0.38–4.02)	4.25 (1.57–11.53)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defects.

There was an imbalance between the 2 groups in terms of fetal echocardiography, with 16.3% of SLE offspring having ≥1 fetal echocardiography compared to 2.5% of control children. When accounting for the possibility of detection bias by excluding children with ≥1 fetal echocardiography (n=331) from the multivariable analyses, adjusted effect estimates were similar to the primary multivariable analysis results for CHD and all subtypes of CHD (Table 5.4).

Table 5.4. Adjusted effect estimates of the risk of all types of congenital heart defects and subtypes in the overall sample of children (n=9212) and subsample excluding children with at least one fetal echocardiography (n=8881), from Quebec's administrative databases, Canada, 1989-2009

Sample	Any CHD OR* (95% CI)	ASD OR* (95% CI)	VSD OR* (95% CI)	Valve Anomalies OR* (95% CI)
All children (n=9212)				
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	2.62 (1.77–3.88)	3.32 (1.97–5.57)	2.50 (1.31–4.75)	2.95 (1.23–7.07)
Excluding children with ≥1 fetal echocardiography (n=8881)				
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	1.95 (1.18–3.23)	2.41 (1.23–4.75)	2.06 (0.96–4.43)	2.32 (0.67–8.05)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

*Adjusted for maternal age, calendar year, sex, education, ethnicity, pregestational diabetes mellitus, gestational diabetes mellitus, hypertension, and asthma.

In the subsample analysis controlling for maternal medications (Table 5.5), though the effect estimates for the association of ASD (OR 2.05, 95% CI 0.66-6.37) with maternal SLE remained similar to the primary multivariable analysis result, the 95% CI was wide and included the null value due to reduced sample size (155 SLE offspring and 1770 controls). In addition, after adjusting for maternal medication exposures, results were inconclusive for the risk of CHD and specifically VSD in SLE offspring compared to controls. However, we observed an effect of corticosteroid exposure on the likelihood of CHD (OR 5.65, 95% CI 1.65-19.34), after adjusting

for both pregestational and gestational diabetes. Of note, we could not perform a multivariable analysis adjusting for medication exposure for the outcome of valve anomaly, as no case was observed in SLE offspring in the subsample with provincial drug coverage.

Table 5.5. Multivariable analyses of the risk of all types of congenital heart defects and subtypes in subsample of children with public drug coverage (n=1925) in Quebec's administrative databases, Canada, 1989-2009

Covariates	Any CHD OR (95% CI)	ASD OR (95% CI)	VSD OR (95% CI)
Maternal SLE			
No	Reference	Reference	Reference
Yes	1.46 (0.53–4.04)	2.05 (0.66–6.37)	1.50 (0.28–8.11)
Sex			
Male	Reference	Reference	Reference
Female	0.88 (0.49–1.57)	0.77 (0.36–1.62)	0.98 (0.37–2.66)
Education			
≤ High school	Reference	Reference	Reference
≥ College	0.87 (0.45–1.68)	1.07 (0.47–2.43)	0.96 (0.33–2.78)
Ethnicity			
White	Reference	Reference	Reference
Other	0.57 (0.27–1.18)	0.66 (0.28–1.58)	0.60 (0.19–1.93)
Pregestational diabetes mellitus			
No	Reference	Reference	Reference
Yes	2.99 (0.96–9.29)	3.72 (0.99–14.00)	4.43 (0.85–23.14)
Gestational diabetes mellitus			
No	Reference	Reference	Reference
Yes	2.23 (0.76–6.55)	1.68 (0.38–7.46)	5.32 (1.40–20.12)
Corticosteroids			
No	Reference	Reference	Reference
Yes	5.65 (1.65–19.34)	3.26 (0.68–15.75)	3.73 (0.43–32.54)
Antimalarials			
No	Reference	Reference	Reference
Yes	0.29 (0.01–5.30)	–	0.60 (0.02–19.96)
Immunosuppressives			
No	Reference	Reference	Reference
Yes	1.77 (0.09–35.98)	–	–
Antidepressants			
No	Reference	Reference	3.29 (0.08–132.49)
Yes	1.12 (0.25–4.92)	0.98 (0.13–7.60)	Reference
Hypertension			
No	Reference	Reference	Reference
Yes	0.36 (0.04–3.43)	0.62 (0.06–6.02)	–
Asthma			
No	Reference	Reference	Reference
Yes	1.79 (0.63–5.04)	0.46 (0.06–3.72)	1.76 (0.32–9.60)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

Among children with CHD, those born to SLE mothers had more CHD repair procedures compared to controls [10.8% (95% CI 2.9-24.8) versus 3.8% (95% CI 1.4-7.9)] (Table 5.6). In addition, compared to controls, offspring of SLE mothers had a substantially increased likelihood of having a repair procedure for any type of CHD (OR 5.82, 95% CI 1.77-19.09), and specifically having a cardiac septal defect repair procedure (OR 4.95, 95% CI 1.22-20.07), after adjusting for relevant covariates.

Table 5.6. Frequency of congenital heart defects with and without repair procedures among SLE offspring and control children (n=9212) in Quebec's administrative databases, Canada, 1989-2009

Types	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
CHDs, n (%)			
All CHDs	37 (5.1)	159 (1.9)	<0.0001
CHDs with repair procedures	4 (0.6)	6 (0.1)	0.005
ASDs, n (%)			
All ASDs	21 (2.9)	68 (0.8)	<0.0001
ASDs with repair procedures	2 (0.3)	3 (0.0)	0.052
VSDs, n (%)			
All VSDs	12 (1.7)	56 (0.7)	0.002
VSDs with repair procedures	1 (0.1)	2 (0.0)	0.22
Cardiac valve anomalies, n (%)			
All valve anomalies	7 (1.0)	26 (0.3)	0.009
Valve anomalies with repair procedures	0 (0)	0 (0)	–

ASD indicates atrial septal defect; CHD, congenital heart defect; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

5.7. Discussion

Compared to children from the general population, children born to women with SLE have an increased risk of CHD, including a specifically increased risk of ASD, VSD, and valve anomalies. In addition, offspring of SLE mothers have substantially increased odds of CHD repair procedures compared to children from the general population. The effect of SLE on all types of CHD does not seem to be explained by detection bias and might be independent of medication exposures. Because of the limited power afforded by the sample of subjects who had provincial drug coverage, the findings of analyses limited to this subgroup are inconclusive, though still pointing to an increased risk of CHD, regardless of medication exposure.

We found an association between in utero exposure to corticosteroids and CHD, although the confidence interval was wide. Several studies have investigated the potential association between in utero corticosteroid exposure and congenital anomalies, but despite a potential and still controversial increased likelihood of oral cleft defects, no excess risk has been seen for other types of congenital anomalies, in particular cardiac.[186] The effect of corticosteroid exposure on CHD observed in our study might be in part explained by confounding by disease severity. Indeed, if SLE itself has a causal effect on CHD (e.g. mediated through inflammation and/or autoantibodies), and women with more severe SLE are more likely to have active disease during pregnancy and require corticosteroids for disease control, then confounding by disease severity is likely to have occurred and account for some of the apparent effect of corticosteroid exposure.

We observed that pregestational diabetes was a potentially important predictor of CHD and all subtypes investigated. It is well recognized that, in the conception period and the first trimester of pregnancy, maternal hyperglycemia can cause diabetic embryopathy resulting in major congenital anomalies.[92] The most frequent type of major congenital anomalies seen in

women with pregestational and gestational diabetes is CHD.[92] Prior studies have shown that the likelihood of CHD was highest in women with pregestational diabetes compared to those with gestational diabetes (respectively 3-fold and 1.5-fold increased risk relative to healthy women).[93,94] We observed similar effect estimates, suggesting that our findings are consistent with published literature on diabetic embryopathy.

The strength of our study resides in the use of Quebec's administrative databases, which collect information on all deliveries performed in the province, allowing us to create OSLER, the largest cohort of children born to mothers with SLE ever assembled. In addition, Quebec's administrative databases are a valid data source for the conduct of observational studies, with prior work from our group showing that our SLE case definition has a very high specificity (0.99).[169] Of note, 16% of SLE children were exposed in utero to antimalarial drugs, which are used to prevent SLE flare. This is comparable to exposure in SLE pregnancies observed over a similar time period and from a well-established tertiary care lupus cohort, where 22% were exposed to antimalarials beyond the first trimester.[45] Furthermore, a recent study assessed the validity of pregnancy-related variables recorded in the RAMQ, MED-ECHO, and ISQ databases, such as gestational age and live births, and showed very high sensitivity (0.97-0.99) and specificity (0.92-0.98) for all the variables examined, concluding that these administrative databases are a valid data source for pregnancy-related variables.[187]

We used a widely accepted definition of CHD based on ICD-10/9 diagnostic codes established by the EUROCAT network.[179] In addition, a recent study assessed the validity of ICD-10/9 diagnostic codes for major congenital anomalies, including CHD, recorded in Quebec's administrative databases.[180] Those investigators used medical chart as the gold standard and evaluated the performance of relevant diagnostic codes recorded during the first year of life in

children born to asthmatic women compared to children born to non-asthmatic women. Results were similar between both groups; in particular, both the positive predictive value of CHD and the negative predictive value for any type of congenital anomalies were high (both more than 94%).[180] As asthma is one of the most frequent chronic diseases encountered during pregnancy, with potential for disease exacerbation, similar to SLE in pregnancy, it is of interest to note that there was no differential ascertainment of congenital anomalies in offspring of affected women compared to controls. We would hope, though we cannot be sure, that there would similarly be no differential ascertainment of congenital anomalies in offspring of women affected by SLE, compared to controls.

Still, we accounted for the possibility of detection bias due to more frequent use of fetal echocardiography in SLE pregnancies, which is a considerable strength of our study. After excluding children who had ≥1 fetal echocardiography, the effect estimates for all types and subtypes of CHD were similar compared to the overall analysis results. However, this sensitivity analysis did not account for subtle forms of detection bias that might have occurred after delivery. Indeed, mothers with SLE might be more concerned that their child develops a health problem than control mothers, and might seek more frequently medical attention for their offspring. If this were the case, it would increase the number of CHD cases diagnosed in children born to SLE mothers, particularly minor and/or asymptomatic cases. To strengthen our case, we found a substantially increased risk of CHD repair procedures in offspring of SLE mothers compared to controls, which does not suggest that detection bias occurring after the pregnancy solely explained the observed association between CHD and maternal SLE.

Our study has some potential limitations. As mentioned previously, the subsample analysis accounting for relevant medication exposures did not allow us to precisely estimate the

association between maternal SLE and CHD in offspring due to the limited power given by the reduced sample of subjects with provincial drug coverage. Regardless, this is the largest study to date assessing the risk of CHD in SLE offspring.

Another potential limitation is that medication exposures were defined based on filled prescriptions, which might not have reflected actual intake. However, it is likely that most women who filled a prescription for a specific medication took at least one dose because, within the RAMQ prescription plan, beneficiaries need to cover part of their medication cost.[188]

In addition, in all observational studies, unmeasured or poorly measured confounding represents a major concern. We have considered this and used well-defined proxies for certain variables (e.g. socio-economic status, race/ethnicity). Still, administrative databases do not contain information on, for example, smoking, obesity, or alcohol use, which have all been associated with an increased risk of having a child with CHD in exposed pregnant women. However, prior data from Quebec suggest that smoking practices, obesity prevalence, and alcohol use in SLE patients are comparable to the general population.[189] Therefore, the lack of information on these variables is unlikely to have introduced substantial bias.

Other limitations include our inability to adjust for folic acid and multivitamin exposures during pregnancy since these supplements are frequently obtained without a prescription (i.e. over the counter), and thus not captured in a large proportion of women covered by the RAMQ-Rx plan. Moreover, stillbirths were not included a priori in our analyses because a significant proportion of births labeled as stillbirths in Quebec result from pregnancy termination, for which no information on the outcome of interest is recorded.[178] Still, in our cohort, we observed few stillbirths resulting from pregnancy termination, and the effect estimate for CHD did not change when stillbirths were included in the overall analysis (see Online Data Supplements).

Furthermore, Quebec's administrative databases do not record serological data on any individual. This would have been of interest particularly in women with SLE to determine if specific types of maternal autoantibodies, such as anti-Ro//SSA and/or antiphospholipid antibodies, predict CHD in children born to women with SLE. Still, establishing an association between in utero SLE exposure and CHD shed new light on the potential role of maternal autoantibodies and cytokines in CHD pathogenesis.

Indeed, maternal SLE-related mechanisms that could be implicated in the physiopathology of CHD in offspring include autoantibody-mediated damage and cytokine imbalance. Transplacental transfer of maternal IgG antibodies begin in the second trimester, reaching circulating levels in the newborn that exceed maternal levels, due to active transport across the placenta.[102] Anti-SSA/Ro and anti-SSB/La antibodies, found in approximately 40% of women with SLE, cross the placenta and are associated with the development of neonatal lupus, with congenital heart block being the most characteristic cardiac manifestation. Investigators have demonstrated that maternal anti-SSA/Ro and anti-SSB/La antibodies bind apoptotic fetal cardiocytes, resulting in the release of pro-inflammatory and pro-fibrosing cytokines, and ultimately scarring.[103] This process likely extends beyond the conduction tissue, involving the myocardium, endocardium and valves. In a recent retrospective analysis of autopsies from 18 cardiac neonatal lupus cases, cardiac histological damage outside of the conduction system was frequently observed.[100] In particular, one autopsy showed a lympho-histiocytic infiltrate with inflammatory giant cells in the ventricular septum, while another displayed foci of microscopic calcification in the atrial septum. Moreover, 40% (6/15) of deaths due to congenital heart block had pathology findings such as fibrosis and calcification of the valves and/or valve apparatus, including the tricuspid, mitral, aortic and pulmonary valves.[100]

Cardiac septation occurs early in embryogenesis and is complete by 6 weeks of gestation.[104] Since transplacental passage of maternal autoantibodies only occur as early as the 20th week of gestation, it is unlikely that maternal autoantibodies directly interfere with cardiac septation. However, muscular VSD, which account for approximately 75% of all VSD, are thought to arise from foci of cellular death that occur during active cardiac remodeling, within an already formed ventricular septum.[105] In addition, maternal autoantibodies might prevent closure of cardiac septal defects that might have closed otherwise, possibly explaining the excess risk of cardiac septal defects in offspring of SLE mothers compared to controls.

Antiphopholipid antibodies (aPL) are another type of autoantibodies commonly found in women with SLE, which also cross the placenta. In a recent study of children born to women with antiphospholipid syndrome, 40% of neonates had positive aPL in cord blood.[106] aPL are strongly associated with valvular disease (e.g. valvular nodules, regurgitation, and verrucous endocarditis) in aPL-positive adult patients with and without SLE. Valvular deposits of aPL in affected adult subjects are thought to play an important pathogenic role in valvular disease.[107] Although prior studies have reported perinatal thrombotic events occurring in children born to aPL-positive mothers, there is currently no data on the prevalence of congenital valve anomalies or other types of CHD in these children.[108] Since aPL are involved in valvular damage in seropositive adult subjects and cross the placenta, it could be hypothesized that they may play a role in valve anomalies in exposed fetuses.

Cytokines, such as transforming growth factor beta (TGF-beta), play an important role in cardiac embryogenesis. In particular, adequate endocardial cushion formation, which is a critical step in cardiac septation, requires expression of TGF-beta.[109] The importance of both maternal and fetal TGF-beta in cardiac embryogenesis has been well illustrated in animal models.[109]

Notably, TGF-beta-1-null mice, born to TGF-beta-1-null mothers, demonstrate severe CHD, while TGF-beta-1-null mice born to wild-type mothers (i.e. with normal expression of TGF-beta-1) do not. Because transplacental transfer of circulating TGF-beta can occur from mother to fetus, investigators hypothesized that maternal TGF-beta-1 might rescue any potential heart defects in the null offspring.[109] Interestingly, in SLE patients, serum levels of TGF-beta-1 are substantially lower than in controls, with levels inversely correlating with disease activity.[110] Thus, maternal TGF-beta rescue of fetuses with defective TGF-beta levels might not occur in women with SLE, potentially accounting for the increased risk of CHD.

In conclusion, children born to women with SLE have an increased risk of CHD, including a specifically increased risk of ASD, VSD, and valve anomalies, compared to children from the general population. In addition, offspring of SLE mothers have substantially increased odds of CHD repair procedures compared to children from the general population. Our findings prompt further research to elucidate the potential role of disease-related factors, such as in utero drug exposures, maternal autoantibodies and cytokines, which might explain the increased likelihood of CHD in children born to mothers with SLE.

5.8. Appendix

5.8.1. Supplemental methods

For this study, we worked in collaboration with the "Régie de l'Assurance Maladie du Québec (RAMQ)" which manages both the MED-ECHO and physician billing databases. The RAMQ employs skilled data analysts, who extracted the data, according to our pre-specified requirements, to create the exact dataset needed for our study. Only information judged useful for the conduct of the study was transmitted to the research team, as data managed by the RAMQ

is highly restricted by the "Commission d'accès à l'information du Québec". Therefore, we only had access to the cohort once it was created. We verified that the cohort conformed to our selection criteria (i.e. appropriate SLE case definition, matching with controls, etc). However, we do not have information on women who were not included in our study and could not produce a flow diagram illustrating the subject selection from the source population.

Stillbirths were not included in our analyses because a significant proportion of births recorded as stillbirths in Quebec result from pregnancy termination, for which no information on the outcome of interest is recorded. In Quebec, information on stillbirths are recorded based on the following definition: death prior to the complete expulsion or extraction from its mother of a product of conception weighing 500 or more grams, regardless of the gestational age.[190] Since pregnancy terminations are performed up to 24 weeks of gestation in Quebec, some fetal deaths are labeled as stillbirths even if they result from a pregnancy termination.

In a matched cohort study, ignoring the matching variables can leave bias if there are additional confounders, even when controlling for these additional confounders. Therefore, control for the matching variables is needed when dealing with matched cohort data, although a matched analysis per se is not required.[191]

Generalized estimating equation methods account for the correlation in outcomes of children born to the same mother (i.e. the probability of a congenital anomaly is higher when a sibling has been affected), with each mother serving as the clustering unit.[184]

Multiple imputation was performed assuming an arbitrary missing pattern, using a multivariable normal approach via the Markov chain Monte Carlo method, and included the same covariates as the primary multivariable model.[195| Multivariable analysis results were very similar using either the dataset with missing data or the imputed dataset.

We compared means between SLE offspring and control children with a t-test and proportions with a chi-square test, unless cells were too sparse, in which case we used a two-sided Fisher's exact test.

5.8.2. Supplemental results

There were 10 stillbirths among 729 SLE births (1.4%, 95% CI 0.7, 2.6) and 49 stillbirths among 8542 control births (0.6%, 95% CI 0.4, 0.8). For all stillbirths, cause of death was identified in the mandatory stillbirth report form. In the SLE group, one stillbirth was due to pregnancy termination, while no stillbirth was attributed to CHD. In the control group, two stillbirths were due to pregnancy terminations, while one stillbirth was attributed to CHD. The effect estimate for CHD did not change when we included stillbirths in the overall analysis (OR 2.80, 95% CI 1.94, 4.04).

5.8.3. Table 5.7. Diagnostic codes for congenital heart defects

Type of congenital anomaly	**ICD*-9 codes**	**ICD-10 codes**
Congenital heart defect	745, 746, 7471- 7474	Q20- Q26 excluding Q24.6, Q25.0
Ventricular septal defect	7454	Q210
Atrial septal defect	7455	Q211
Cardiac valve anomaly	746.0-746.6	Q22, Q23

*International Classification of Diseases (ICD)

5.8.4. Table 5.8. Race/ethnicity definitions

Race/Ethnicity	**Definition**
Caucasian	If both maternal and paternal birthplaces are in Canada, Unites States, or Europe (excluding Spain) with language at home and maternal language being English, French, or another language spoken in Europe (excluding Spanish)
Other	If both maternal and paternal birthplaces are not in Canada, United States, nor Europe (excluding Spain) and/or If language at home and maternal language is not English, French, or another language spoken in Europe (excluding Spanish)

5.8.5. Table 5.9. Repair procedure codes

Type of congenital anomaly	**Repair procedure codes***
Congenital heart defects	47.01-47.97
Cardiac septal defects	47.51-47.55, 47.61-47.64, 47.71-47.74, 47.95
Cardiac valve anomalies	47.01-47.29, 47.96, 47.97

*Reference: Classification canadienne des actes diagnostiques, thérapeutiques, et chirurgicaux. Institut canadien d'information sur la santé - CCI. 2004. http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=codingclass_cci_f (last accessed March 4th, 2014)

5.9. Supplemental material for manuscript #5

5.9.1. Adjusting for birth order

In manuscripts #3 and #4, we have shown that women with SLE have fewer children than women from the general population. Thus, in manuscript #5 (and as well in manuscript #6 described later), selecting the first identified child born after SLE diagnosis may over-sample children from lower birth order in the SLE group compared to the control group. Since a woman having a first child with an adverse outcome may be less likely to have a subsequent pregnancy (hence a child from a higher birth order), birth order differences between our two study groups may lead to overestimation of the risk of maternal SLE on offspring outcomes. Therefore, in the multivariate analyses pertaining to manuscript #5 (as well as manucsript #6, described later), we

have controlled for birth order. However, to ensure that we were not introducing selection bias by adjusting for birth order, which can occur when a covariate is affected by the exposure, we compared the SLE effect estimate obtained with the multivariate analysis including and excluding birth order.[195] For both outcomes (i.e. CHD and autism spectrum disorders), the SLE effect estimates were almost identical for the analyses with and without birth order as a covariate.

5.9.2. Use of generalized estimating equation for correlated reproductive outcomes

As mentioned in Chapter 4.1.8, when dealing with reproductive outcomes, we need to account for correlation between observations in our statistical analyses and different approaches can be used to do so.[162, 192] In manuscript #5, we used the GEE methodology to appropriately account for correlation in outcomes of children born to the same mother. Models estimated with a GEE are called "semiparametric" since they are not fully specified by parameters.[184,192] Indeed, using a GEE, we need to specify a functional form for the marginal mean and a functional form for the correlation between observations from the same cluster (i.e. observations from children born to the same mother). Thus, we do not need to fully model the correlation between observations from the same cluster.[184] Parameters can then be estimated by a set of estimating equations defined by the specification of these two functional forms. The most comon choices for correlation structure include the following: independent (i.e. no intracluster correlation), exchangeable (i.e. constant correlation independent of time separation between observations), autoregressive (i.e. correlation decreasing exponentially with time separation between observations), and unstructured (i.e. free correlation specification).[184.192] As discussed in the supplemental material to manuscript #3, the Huber-White method uses GEE

assuming an independent correlation structure.[167] In manuscript #5, we used an exchangeable correlation structure to model correlation between observations in our model estimated with GEE, providing the best Quasi-Akaike Information Criterion (QIC). An important advantage of the GEE method is that the specification of the correlation structure does not need to be correct.[184] Power is increased if the correlation structure is appropriately chosen, but standard error estimates for the parameters are still valid even if the correlation structure is misspecified.[192]

Since the parameters are estimated with marginal methods, we need to interpret them marginally (i.e. at a population-average level), as comparing the average in an exposed group versus an unexposed group.[184] For example, in manuscript #5, the interpretation of the effect estimate that we observed for the risk of CHD in SLE offspring compared to control children should be interpreted as follows: in a group of children born to women with SLE, there is a two-fold increase in the risk of CHD compared to a group of children born to unaffected mothers.

However, the GEE method requires stronger assumptions regarding missing data, in particular that incomplete data are missing completely at random (MCAR), since it does not specify the full conditional likelihood.[184,192] In the presence of data missing at random (MAR), one can still use GEE provided that an appropriate method to deal with data missingness is used.[193] One such approach is multiple-imputation GEE (MI-GEE), which refers to first using multiple imputation to impute full datasets.[193] Then, the missing-data mechanism (i.e. MCAR or MAR) can be further ignored by using the imputed and now complete datasets in the model estimated with GEE and approprately combining the effect estimates.. Misspecification of the multiple imputation (MI) model will only affect the unobserved (i.e. imputed) data but not the observed data. Investigators have shown that if the imputation model is not exaggeratedly

misspecified, this method will perform well. and is relatively robust against model misspecification compared with another approach called weighted GEE (WGEE), which also allows use of GEE under MAR.[193] This method weights observations by the inverse probability of being observed using a prespecified model. Since all subjects are given weights, any misspecification of the model assigning weights will affect all subjects, and will tend to have a larger impact on the results.[193] As described in manuscript #5, we have used MI-GEE, performing multiple imputation (assuming data were MAR) to obtain complete datasets prior to using GEE and then combining the effect estimates.

5.9.3. Sensitivity analyses for unmeasured confounding

As mentioned in the Discussion section of manuscript #5, unmeasured (or poorly measured) confounding always represents a major concern in observational studies. We have considered this and used well-defined proxies for certain variables (e.g. race/ethnicity). Still, administrative databases do not contain information on, for example, smoking, alcohol use, or obesity. To investigate the potential impact of unmeasured confounders, we performed the following sensitivity analyses, even if prior data from Quebec are reassuring, suggesting that smoking practices, obesity prevalence, and alcohol use in SLE patients are comparable to the general population.[189]. Taking maternal obesity as an example of unmeasured confounder, we determined how large the maternal SLE-obseity association in our cohort would have to be so that adjusting for maternal obesity during pregnancy would remove an apparent maternal SLE-outcome association (e.g. effect of maternal SLE on CHD). Using previously developed formulas,[194] we assumed different combinations of values for: 1) the SLE-specific associations of maternal obesity with the outcome CHD, and 2) the SLE-specific prevalence of

exposure to maternal obesity (Table 5.10). We used 2 estimates of SLE-specific prevalence of exposure to maternal obesity: one based on a previous study conducted in Quebec (i.e. 30% in SLE offspring versus 23% in controls) and an another from an overestimation of the prevalence in SLE offspring (40% in SLE offspring versus 20% in controls).[189] As shown below in Table 5.10, since the values for the SLE-specific associations of maternal obesity with CHD and the SLE-specific prevalence of exposure to maternal obesity both need to be large to substantially bias toward the null the maternal obesity-adjusted SLE-CHD association, it is reasonable to conclude that it is unlikely that the unadjusted association is mainly due to the unmeasured confounder.[194]

Table 5.10. Sensitivity of externally adjusted maternal SLE-CHD odds ratio to choice of maternal obesity prevalences among SLE offspring and control children, and SLE-specific maternal obesity-CHD odds ratio

Prevalence of maternal obesity in SLE offspring	Prevalence of maternal obesity in controls	OR for maternal obesity and CHD association		
		2.8	5.0	10.0
30%	23%	2.6	2.6	2.5
40%	20%	2.3	2.1	1.7

In summary, the creation of our large population-based cohort OSLER allowed us to determine that SLE offspring have a substantially increased risk of CHD compared to children from the general population. OSLER provides a unique opportunity to investigate long-term health outcomes, such as autism spectrum disorders, in SLE offpsring, which will be the focus of the next Chapter.

6. Autism spectrum disorders in children born to women with SLE

6.1. Preamble to manuscript #6

In manuscript #6, we use OSLER to evaluate if children born to SLE mothers have an increased risk of autism spectrum disorders compared to children born to unaffected mothers.[18] As there is no gold standard for the diagnosis of autism spectrum disorders, particularly in the setting of administrative database research, we use Bayesian latent class models to adjust the SLE effect estimate for the risk of autism spectrum disorders for imperfect case ascertainement. This manuscript, entitled "Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: results from the OSLER cohort", is currently under consideration for publication by Arthritis & Rheumatology.

6.2. Title page

Title: Increased Risk of Autism Spectrum Disorders in Children Born to Women with Systemic Lupus Erythematosus: Results from the OSLER Cohort

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Keywords: Systemic lupus erythematosus; autism spectrum disorders; pregnancy

Word Count: 2836

6.3. Abstract

Importance: *In utero* exposure to maternal antibodies and cytokines are potential risk factors for autism spectrum disorders. To date, no one has assessed the risk of autism spectrum disorders in offspring of mothers with systemic lupus erythematosus (SLE).

Objective: To determine if children born to mothers with SLE have an increased risk of autism spectrum disorders compared to children born to mothers without SLE.

Design: The "Offspring of SLE mothers Registry (OSLER)" is a large population-based, historically prospective cohort study (01/1989-12/2009).

Setting: Universal healthcare databases in Quebec.

Participants: We identified all women who had ≥1 hospitalization for delivery after SLE diagnosis, and a randomly selected control group of women, matched ≥4:1 for age and year of delivery. We identified children born live to SLE mothers and their matched controls (respectively 719 and 8493 children).

Main outcome and measure: International Classification of Diseases diagnosis of autism spectrum disorders in Quebec's hospitalization and physician billing databases.

Results: Children born to women with SLE had more records of autism spectrum disorders compared to controls [1.4% (95% CI 0.8,2.5) versus 0.6% (95% CI 0.5,0.8), difference 0.8% (95% CI 0.1,1.9)]. Mean age at autism spectrum disorder diagnosis was younger in offspring of SLE mothers (3.8 years, 95% CI 1.8,5.8) as opposed to controls (5.7 years, 95% CI 4.9,6.5). In primary multivariate analysis, controlling for parental demographics, sex and birth order of child, and maternal comorbidities, SLE offspring had substantially increased risk of autism spectrum disorders versus controls (OR 2.19, 95% CI 1.09,4.39). In a sensitivity analysis further adjusting for obstetrical complications, the estimated effect of SLE remained similar (OR 1.97, 95% CI 0.95, 4.08), although the 95% CI included the null value

Conclusion and Relevance: Compared to children from the general population, children born to women with SLE have an increased risk of autism spectrum disorders, although in absolute terms it represents a rare outcome. These hypothesis-generating data provide direction for additional studies of maternal autoimmunity and autism spectrum disorder risk.

6.4. Introduction

In North America, autism spectrum disorders (ASD) affect 0.5-1% of school-age children.[111,112] Systemic lupus erythematosus (SLE) is a multi-system disease, which predominantly occurs in women during their childbearing years. Children born to women with SLE may have an increased risk of neurodevelopmental disorders versus children born to healthy women. However, the evidence is limited, based on only a handful of small observational studies.[8-12,113] Moreover, none of these studies has specifically evaluated the risk of ASD.

Recent experimental data suggest *in utero* exposure to maternal antibodies and cytokines as important risk factors for ASD.[114,196] Interestingly, women with SLE display high levels of autoantibodies [e.g. anti-N-methyl-D-aspartate receptor (NMDAR) antibodies] and cytokines [e.g. interleukin-6 (IL-6)], which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring.[140,149] Furthermore, subjects with SLE and ASD share a common genetic predisposition to the C4B null allele, which could impair the fetal immune response to *in utero* immunologic insults.[117-119] Moreover, SLE pregnancies are at increased risk of adverse obstetrical outcomes, such as prematurity and small for gestational age (SGA), and medication exposures, such as anticonvulsants, which have been implicated as potential risk factors for ASD.[121,122, 197]

Based on these available data and since children exposed *in utero* to SLE face several potential risk factors for neurodevelopmental disorders, we aimed to evaluate, in a large population-based study, if offspring of mothers with SLE have an increased risk of ASD compared to children born to mothers without SLE.

6.5. Methods

6.5.1. Study cohort

The "Offspring of SLE mother Registry (OSLER)" is a population-based cohort of 719 children born to mothers with SLE, matched to 8493 control children. To create this large cohort, we identified all women with SLE who had ≥1 hospitalization for a delivery (either for a stillbirth or live birth) in the interval between 01/1989 and 12/2009, using data from MED-ECHO ("Maintenance et exploitation des données pour l'étude de la clientèle hospitalière") 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, and provides, for each hospitalization, a primary discharge diagnosis and up to 15 non-primary diagnoses, captured as International Classification of Diseases (ICD)-9 codes (and since 2006, ICD-10 codes). RAMQ billing database records one physician-assigned diagnosis, based on ICD-9 codes, for each physician encounter.

6.5.2. In utero exposure to SLE

Women were identified as SLE cases (based on a validated definition,[169] using 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. From these databases, a general population control group was composed of women matched ≥4:1 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 a specific identifying number, present in every child's file in the databases, leading to very few linkage failures (<2%). Those children born live were the basis of the OSLER cohort for outcome ascertainment and long-term follow-up in our current study, one being the exposed group consisting of children born to women with SLE, and the other being the control group consisting of children born to women without SLE.

6.5.3. Autism spectrum disorders ascertainment

The cohort of children was linked to determine hospitalizations and all diagnoses throughout the observation interval. This cohort interval 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. ASD), age 18, death, or end of study (i.e. 31/12/2009).

We ascertained ASD in offspring based on a previously validated definition requiring the presence of at least one relevant diagnostic code (i.e. ICD-9 code 299 or ICD-10 codes F84.0, F84.1, F84.3, F84.5, F84.8, F84.9, which encompass autistic disorder, atypical autism, childhood disintegrative disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified) in the hospitalization or physician billing databases.[198]

6.5.4. Assessing relevant covariates

For all mothers in our study, we reviewed the MED-ECHO and RAMQ data to identify specific pre-existing and current co-morbidities (i.e. pregestational diabetes, asthma, depression) recorded in the 2 years prior to (and including) the time of delivery, as well as obstetrical complications, such as preterm birth, at the time of the hospitalization for delivery. The diagnosis of specific co-morbidities and obstetrical complications was based on ICD-9/10 codes indicating

≥1 hospitalization or ≥2 physician visits (≥8 weeks apart) for the diagnosis of interest, as per previously validated methodology.[181,182]

The "Institut de la statistique du Québec (ISQ)" provided data on the demographics of the parents at the time of delivery, including maternal education and paternal age, as well as maternal and paternal birthplace, maternal language, and language spoken at home, which were used to establish the race/ethnicity of the offspring (eTable 1 shows race/ethnicity definition). In addition, we obtained data on birth order, infant birth weight, and gestational age, allowing determination of SGA babies (i.e. birth weight below the 10^{th} percentile Canadian statistics for gestational age)[199] and premature births (i.e. babies born before 37 weeks gestation).

Comprehensive and valid data on drug exposures is available from the RAMQ prescription database, but only for beneficiaries of the public drug plan,[183] which covers recipients of social assistance, and workers and their families who do not have access to a private drug insurance program. In our cohort, 22% of exposed children and 21% of controls were born to a mother with public drug coverage throughout pregnancy.

In this subgroup, we obtained all information on the prescription of certain types of medications, including corticosteroids (i.e. oral or intravenous corticosteroids), antimalarials (i.e. hydroxychloroquine or chloroquine), immunosuppressives (i.e. azathioprine, mycophenolate mofetil, mycophenolate sodium, and methotrexate), and any types of anticonvulsants and antidepressants. We used gestational age at birth to calculate back to the estimated start of the gestational period, then determined whether a medication exposure of interest ever occurred during pregnancy (based on ≥1 prescription filled during gestation).

6.5.5. 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. ASD), for children born to women with SLE, relative to the control group. We assessed the robustness of our effect estimates by conducting exploratory Cox proportional hazard analyses with frailties, which provided similar results. These analyses were performed using the R software version 2.15.1 (Copyright 2012 The R Foundation for Statistical Computing).[200]

Data were missing for the variables education and race/ethnicity, in, respectively, 5.6% and 1.7% of subjects. Information on education and race/ethnicity is collected at the time of delivery when parents complete the birth certificate, which is sent to the ISQ and used for demographic statistics. Non-Caucasian mothers might have been less likely to provide information on education due to language barrier. Indeed, we observed 8.6% of missing values on education in non-Caucasisan subjects compared to 4.4% in Caucasian subjects. Thus, we assumed that data were missing at random (MAR) i.e. the probability that information on a variable is missing is not dependent on unobserved values. We used multiple imputation to handle missing data, using the Multivariate Imputation by Chained Equations (MICE) program in R.[201] The imputation model used logistic regression and included, in addition to education and race/ethnicity (as dependent variables), the following independent variables: maternal age, sex of child, calendar year of delivery, birth order, maternal SLE status and comorbidities (i.e. asthma and pregestational diabetes), as well as obstetrical complication (i.e. gestational diabetes). Moreover, we performed a sensitivity analysis with and without the imputed datasets, showing similar results.

In primary multivariate analysis, we matched exposed and unexposed subjects for maternal age and calendar year of delivery, but we also further adjusted for maternal age and calendar year to control for potential residual confounding by these variables. In addition, we adjusted for birth order as well as relevant demographic factors and maternal co-morbidities, including: sex of child, maternal education, child's ethnicity/race, depression, asthma, and pregestational diabetes. After considering all these covariates in both univariate and multivariate models, we excluded depression from the final multivariate model because no ASD case was recorded for this covariate.

As we aimed to estimate the overall effect of *in utero* SLE exposure on the risk of ASD, we did not adjust for obstetrical complications in our primary multivariate analysis since obstetrical complications, such as gestational diabetes, preterm birth, and SGA, are potentially on the causal pathway between *in utero* SLE exposure and the outcome ASD.[195] Moreover, adjustment for obstetrical complications might bias the SLE effect estimate if there are unmeasured common causes of obstetrical complications (e.g. SGA) and ASD.[195] Nevertheless, we performed a sensitivity analysis, further controlling for obstetrical complications (i.e. gestational diabetes, preterm birth, and SGA), and compared the SLE effect estimate to the one obtained in primary multivariate analysis (i.e. if the estimates are similar, this suggests absence of substantial bias).

In the sub-sample with public drug coverage, due to the reduced number of subjects precluding a multivariate analysis, we used descriptive statistics to assess *in utero* maternal medication exposures described previously.

When outcomes are defined by ICD codes within administrative data, one must be aware that the diagnoses are not necessarily clinically confirmed. Without easy access to a gold standard for case definition, the true disease state for each subject is unknown ('latent'), and

sensitivity and specificity of a single diagnostic definition cannot be directly estimated. One can, however, use various case definitions in Bayesian latent class models, with each available method of case ascertainment contributing some information about the case status of each individual.[202] With Bayesian latent class models, instead of trying to identify a 'disease case' (or outcome) with certainty, subjects are assigned a *probability* of being a disease case, based on prior inputs about the sensitivity and specificity of one or more diagnostic tests and their case ascertainment data.[202] Thus, in further sensitivity analyses, we used this approach to account for the imperfection in case ascertainment from each of our 2 methods, billing and hospitalization diagnoses. Based on a previous study assessing the validity of ASD case definitions using administrative data, we assumed a range of sensitivities and specificities for hospitalization (sensitivity 5-45%, specificity 90-100%) and physician billing (sensitivity 65-95%, specificity 80-100%) diagnoses, input to the model as prior information.[198] We also used less informative priors to check the robustness of our parameter estimates. We fit a Bayesian latent class hierarchical regression model to provide estimates of ASD risk, sensitivities and specificities of the case definitions. The first level of the model accounted for sampling variability in ASD risk, correlation between siblings (by adding a cluster term for each mother), and for errors in the 2 case ascertainment methods. These were represented by binomial distributions in which the probability of a positive test adjusted for the sensitivity and specificity of each method of ascertainment. We also added a term to estimate the possible dependence of the 2 case definitions.[203] The second level of the model accounted for variations in ASD risk according to maternal demographics (age and education) and co-morbidities (asthma and pregestational diabetes), sex of child, birth order, and calendar year of delivery, which were derived from a logistic regression model on the binomial probabilities from the first level. For

each parameter estimate, we calculated a 95% credible interval (95% CrI), the Bayesian analogue to frequentist confidence intervals (CIs). WinBUGS (Version 1.4.3, MRC Biostatistics Unit, University of Cambridge, Cambridge, UK) was used to fit these models.[204]

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. The first author takes full responsibility for the accuracy and completeness of the data.

6.6. Results

509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age and mean SLE disease duration were respectively 30.3 (standard deviation, SD, 5.0) and 3.7 (SD 4.0) years (Table 6.1). Mothers with SLE had similar demographic characteristics compared to control mothers, except for race/ethnicity as they were less likely to be Caucasian. In addition, mothers with SLE had more co-morbidities and experienced substantially more obstetrical complications, such as preterm births and SGA babies, compared to control mothers. *In utero* drug exposures were more frequent in SLE offspring compared to controls, with exposures to corticosteroids and antimalarials being the most common drugs prescribed during SLE pregnancies.

Table 6.1. Characteristics of the cohort (n=9212)

Characteristics	SLE offspring (n=719)	Control children (n=8493)
Maternal characteristics		
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)
Paternal characteristics		
Mean age, years (sd)	33.2 (5.8)	33.3 (5.9)
Demographic characteristics		
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)
Obstetrical characteristics		
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)
In utero medication information		
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]

[a]Denominator used for proportion is number of children born to systemic lupus erythematosus (SLE) mothers with public drug coverage during pregnancy; [b]denominator used for proportion is number of children born to control mothers with public drug coverage during pregnancy

Children born to women with SLE had more records of ASD diagnoses compared to controls [1.4% (95% CI 0.8, 2.5) versus 0.6% (95% CI 0.5, 0.8), difference 0.8% (95% CI 0.1, 1.9)]. In terms of absolute rate events, ASD was still a relatively infrequent occurrence with 63 cases identified (10 among SLE children and 53 among controls) over 83 753 person-years of follow-up, resulting in an incidence rate of 75.2 per 100 000 person-years.

In both groups of children, most ASD diagnoses were registered in the RAMQ billing database, with psychiatrists most frequently recording the diagnosis (in 59% of the cases), while approximately a fourth of the cases had at least one hospitalization with a ASD diagnosis (Table 6.2). Mean age at ASD diagnosis was younger in offspring of SLE mothers (3.8 years, 95% CI 1.8, 5.8) as opposed to controls (5.7 years, 95% CI 4.9, 6.5).

Table 6.2. Sources of autism spectrum disorder records among cases (n=63)

Databases	**SLE cases n=10 (%)**	**Control cases n=53 (%)**
MED-ECHO only	1 (10)	3 (6)
MED-ECHO and RAMQ physician billing	2 (20)	10 (19)
RAMQ physician billing only	7 (70)	40 (75)

[a]MED-ECHO, "Maintenance et exploitation des données pour l'étude de la clientèle hospitalière") ;
[b]RAMQ, "Régie de l'assurance maladie du Québec"

The unadjusted OR of ASD in children born to women with SLE compared to control children was 2.25 (95% CI 1.13, 4.45). In primary multivariate analysis, children born to women with SLE had substantially increased risk of ASD versus controls (OR 2.19, 95% CI 1.09, 4.39) (Table 6.3). In the sensitivity analysis further adjusting for gestational diabetes, preterm birth, and SGA, the SLE effect estimate remained similar (OR 1.97, 95% CI 0.95, 4.08), although the 95% CI included the null value (Table 6.3). In addition to maternal SLE, other potential predictors of ASD included gestational diabetes (OR 2.42, 95% CI 0.93, 6.26) and SGA (OR 1.69, 95% CI 0.84, 3.43), although wide confidence intervals precluded definitive conclusions about these variables. Of note, male sex was a strong predictor of ASD in multivariate analyses (primary analysis OR 3.96, 95% CI 2.10, 7.47).

Table 6.3. Univariate and multivariate analyses of the risk of autism spectrum disorders (SLE offspring versus controls (n=9212)

Covariates	Univariate OR[a] for ASD (95% CI)	Primary multivariate OR[a] for ASD (95% CI)	Multivariate OR[a] for ASD including obstetrical complications (95% CI)
Maternal SLE			
No	Reference	Reference	Reference
Yes	2.25 (1.13, 4.45)	2.19 (1.09, 4.39)	1.97 (0.95, 4.08)
Sex of child			
Female	Reference	Reference	Reference
Male	4.01 (2.13, 7.56)	3.96 (2.10, 7.47)	3.85 (2.03, 7.30)
Birth order			
1	Reference	Reference	Reference
≥ 2	0.80 (0.47, 1.35)	0.82 (0.47, 1.44)	0.84 (0.48, 1.48)
Race/ethnicity			
Other	Reference	Reference	Reference
Caucasian	1.04 (0.59, 1.83)	1.06 (0.60, 1.89)	1.07 (0.60, 1.92)
Education			
High school or less	Reference	Reference	Reference
College or more	0.76 (0.46, 1.25)	0.77 (0.45, 1.29)	0.82 (0.48, 1.40)
Asthma			
No	Reference	Reference	Reference
Yes	1.07 (0.26, 4.39)	1.10 (0.26, 4.61)	1.09 (0.26, 4.62)
Pregestational diabetes			
No	Reference	Reference	Reference
Yes	0.88 (0.12, 6.47)	0.83 (0.11, 6.26)	0.89 (0.12, 6.71)
Gestational diabetes			
No	Reference	_____	Reference
Yes	2.61 (1.03, 6.62)		2.42 (0.93, 6.26)
Preterm birth			
No	Reference	_____	Reference
Yes	1.40 (0.64, 3.08)		1.12 (0.49, 2.55)
Small for gestational age			
No	Reference	_____	Reference
Yes	2.00 (1.01, 3.96)		1.69 (0.84, 3.43)

[a]Matching and adjusting for maternal age and calendar year; odds ratio (OR); confidence interval (CI); systemic lupus erythematosus (SLE)

In the subsample of children with drug coverage (including 155 SLE offspring and 1770 controls), *in utero* medication exposures were rare in the 18 ASD cases (2 born to SLE mothers and 16 born to control mothers): none were exposed to antimalarials, antidepressants, nor immunosuppressants, while only one case born to a SLE mother and another born to a control mother were respectively exposed to corticosteroids and anticonvulsants.

In Bayesian latent class analyses, accounting for all sources of uncertainty about case ascertainment, the unadjusted (OR 2.67, 95% CrI 0.98, 6.47) and adjusted (OR 2.47, 95% CrI 0.88, 6.07) effect estimates for SLE were similar to the estimates from the primary analysis, although the credible intervals were wider and overlapped with the null value.

6.7. Discussion

Within the largest cohort of SLE offspring ever assembled, we observed that children born to SLE mothers had more than a two-fold increase in the risk of ASD. We also demonstrated that the effect of maternal SLE on the risk of ASD was potentially independent of obstetrical complications.

There was a trend for younger age at ASD diagnosis in offspring of SLE mothers versus controls, although the small number of events limited accuracy of this estimate. Still, this raises concerns as to whether there might be a different clinical presentation of ASD in children born to SLE mothers (e.g. earlier and/or more severe disease presentation) versus control children. An alternative explanation might be earlier consultations to healthcare professionals by SLE mothers, either due to the fear that their disease might have affected their child during pregnancy or from more frequent contacts with the healthcare system. However, in a recent study from our group within the same cohort of children, mean age at attention deficit hyperactivity disorder

(ADHD) diagnosis was substantially older in offspring of SLE mothers (12.5 years, 95% CI 11.7, 13.3) as opposed to controls (7.8 years, 95% CI 7.5, 8.1).[205] That finding does not suggest that mothers with SLE consult more promptly than control mothers, and might potentially point toward a different ASD phenotype in SLE offspring.

Obstetrical complications are recognized risk factors for ASD. In the present study, the direction and magnitude of the effect estimates observed for obstetrical complications, including gestational diabetes and SGA as independent predictors of ASD were in accordance with findings from prior population-based studies.[197,206,207] Still, due to the limited number of events, the confidence intervals associated with these effect estimates included the null value. We also observed that male sex was associated with a four-fold increase in the risk of ASD as consistently reported in published literature.[208]

Quebec's administrative databases contain information on all deliveries performed in the province of almost 8 million residents, providing enough power to assess a rare event, such ASD, and allowing us to appropriately control for obstetrical complications. In addition, 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).[169] Of note, 16% of SLE children were exposed *in utero* to antimalarial drugs, which is comparable to exposure in SLE pregnancies observed over a similar time period and from a well-established tertiary care lupus cohort, where 22% were exposed to antimalarials beyond the first trimester.[45] Furthermore, a recent study evaluated the validity of obstetrical variables recorded in the RAMQ, MED-ECHO, and ISQ databases, such as birth weight, gestational age, and live births, and showed very high sensitivity (0.97-0.99) and specificity (0.92-0.98) for all the

variables examined, concluding that these administrative databases are a valid data source for obstetrical variables.[187]

Moreover, we used an ASD case definition, which showed high specificity in our Bayesian latent class analyses (at least 99.7%, 95% CrI 99.5, 99.9). Thus, it is unlikely that a substantial fraction of subjects without a clinically confirmed ASD diagnosis were identified as ASD cases in our study. Yet, we accounted for imperfect case ascertainment in Bayesian latent class models, which provided estimates that still pointed toward a potentially increased risk of ASD in SLE offspring.

Our study has potential limitations. First, we only had information on *in utero* drug exposures in the subsample of children with maternal drug coverage throughout pregnancy, representing approximately 20% of the entire cohort. Although medication exposures were rare in ASD cases within this subsample, we cannot definitively conclude that the effect of SLE on the risk of ASD is completely independent of maternal medications.

Furthermore, in all observational studies, unmeasured (or poorly measured) confounding always represents a concern. We have considered this and used well-defined proxies for certain variables (e.g. race/ethnicity). Still, administrative databases do not contain information on, for example, smoking and obesity, which have been associated with a slightly increased risk of having a child with ASD in exposed pregnant women.[207,209] However, prior data from Quebec suggest that smoking practices and the prevalence of obesity in SLE patients are comparable to the general population.[189] Therefore, the lack of information on smoking and obesity is unlikely to have introduced substantial bias.

Quebec's administrative databases do not record serological data on any individual. This would have been of interest particularly in women with SLE to determine if specific types of

maternal autoantibodies, such as anti-DNA antibodies (a subset of which are anti-NMDAR antibodies), predict ASD in children born to women with SLE.[140] Still, establishing an association between *in utero* SLE exposure and ASD shed new light on the potential role of maternal autoantibodies in ASD pathogenesis.

In summary, compared to children from the general population, children born to mothers with SLE appear to have more than a two-fold increase in the risk of ASD. The effect of maternal SLE on the risk of ASD is potentially independent of obstetrical complications. Our study findings prompt future research, notably on the role of maternal SLE-related autoantibodies, which could yield important insights into the physiopathology of these complex disorders.

6.8. Appendix

Table 6.4. Race/ethnicity definitions

Race/Ethnicity	**Definition**
Caucasian	If both maternal and paternal birthplaces are in Canada, Unites States, or Europe (excluding Spain) with language at home and maternal language being English, French, or another language spoken in Europe (excluding Spanish)
Other	If both maternal and paternal birthplaces are not in Canada, United States, nor Europe (excluding Spain) and/or If language at home and maternal language is not English, French, or another language spoken in Europe (excluding Spanish)

6.9. Supplemental material for manuscript #6

6.9.1. Use of random effect models for correlated reproductive outcomes

In this study, we explored two different approaches to model the outcome of interest (i.e. autism spectrum disorders): the GEE method, discussed previously in Chapter 5, and a random effect model, for which we review the underlying concepts in the next paragraphs.

Random effect models account for correlation by explicitly modeling the between-siblings (or more precisely between-"sets of siblings") random variation and the within-siblings random variation.[162,192] This is done by specifying a hierarchy of distributions within the multivariate model. Using the outcome of interest, autism spectrum disorders, in manuscript #6 as an example, a logistic regression model could be fitted within all children from each set of siblings (within-siblings level) by specifying that $\mathbf{logit\ (p_{ij}) \rightarrow \beta_{0j} + \beta_{1j} * sle_{ij} + \beta_{2j} * mat.age_{ij} + \ldots}$

$+ \beta_{kj} * \mathbf{k}_{ij}$, where **ij** indicates the i^{th} child in the j^{th} mother and where $\mathbf{ASD}_{ij} \sim \mathbf{Bern}\ (p_{ij})$.[192] Then, between-siblings (or more precisely between-"set of siblings") variation around the intercept could be modeled by $\beta_{0j} \sim \mathbf{Normal}\ (\mu_{0j}, \sigma^2)$.[192]

Random effect models can also be applied to Cox proportional hazards analyses by adding a random effect term, called the "frailty".[210] Frailties are unobserved random factors shared by all members (i.e. children) of the same cluster (i.e. mother), and are assumed to follow a given statistical distribution (often the gamma distribution, with support on $[0,\infty)$, mean equal to 1 and unknown variance).[210] We applied this type of model in manuscript #6, where, conditional on the frailty term $\mathbf{b}_j$, the hazard function λ_{ij} followed the usual proportional hazards form: $\lambda_{ij}(t) \rightarrow \lambda_0 \exp(\beta_{1j} * \mathbf{sle}_{ij} + \beta_{2j} * \mathbf{mat.age}_{ij} + \ldots + \beta_{kj} * \mathbf{k}_{ij} + \mathbf{b}_j),\ t > 0$ where **ij** indicates the i^{th} child in the j^{th} mother, λ_0 is the baseline hazard, and $\mathbf{b}_j$ is the frailty term $\sim \mathbf{Gamma}\ (1, \sigma^2_{unknown})$.[210]

Although the interpretation of the effect estimates is different between random effect models and GEE, the actual values of the effect estimates are the same in linear models. However, in logistic and other nonlinear models, the effect estimates are not equivalent, and usually for positive coefficients, the population-average coefficients are more conservative than the subject-specific coefficients.[184] Moreover, random effect models assume that we correctly specify the random effects and their distributions. Marginal models are more robust to these misspecifications because they do not rely on specification of the random effects structure.[184]

Moreover, by using Cox proportional hazards frailty models, conditional on the frailty term, we assume that: 1) the hazard ratio is constant over time and 2) censoring is uninformative.[210] Death was a rare event in OSLER and did not seem to be differential between SLE offspring and control children, occurring in respectively 0.8% (95% CI 0.3, 1.9)

and 0.5% (95% CI 0.4, 0.7). Thus, we believe that censoring was uninformative. However, as we have shown that autism spectrum disorders tended to occur at a younger age in SLE offspring compared to controls, we anticipated that the first model assumption was not met. Indeed, when we tested the proportionality assumption of our model using the cox.zph function in R, we observed evidence of non-proportional hazards for SLE (although all other covariates and the gobal test of proportionality did not show evdence of non-proportionality).[211] Therefore, we chose the GEE method to model the risk of autism spectrum disorders in SLE offspring compared to controls as the mean follow-up time between both exposed and unexposed was similar, and the GEE approach offers advantages, such as producing effect estimates robust to the misspecification of the correlation structure (which we specified as exchangeable in the present study) and conservative compared to those calculated via random effect models, which imply that the SLE effect estimate for the risk of autism spectrum disorders is closer to the null than if we had used a random effect model.[184]

7. Conclusion

SLE can influence not only obstetrical events, but also the number of children born to affected mothers and their long-term outcomes. This thesis research, by using appropriate methods to analyze information from a large SLE cohort and administrative databases, provides the first answers to the question many women with SLE ask: "Will my disease impair my capacity to have children and affect the future health of my children?"

In particular, in manuscripts #3 and #4, we have demonstrated that women with SLE appear to have reduced live birth rates compared to the general population, particularly after diagnosis, using SIR. In addition, we investigated potential predictors of live births in women with SLE and demonstrated that prior hospitalization for SLE was an important predictor of reduced live births. However, we were unable to establish an independent effect of renal disease and antiphospholipid syndrome on live birth rates, as our definitions might have lacked respectively of sensitivity and specificity. Additional studies are needed to clarify the relative importance of factors affecting live birth rates in women with SLE.

Furthermore, we have shown that SLE offspring have an increased risk of CHD (manuscript #5) and autism spectrum disorders (manuscript #6) compared to children from the general population. We demonstrated this by using Quebec's administrative databases and assembling OSLER, the world's largest cohort of children born to mothers with SLE, which provides, with its large sample size and historically prospective study design, a unique opportunity to assess rare long-term health outcomes in SLE offspring. In manuscript #5, assessing the effect of maternal SLE on CHD risk, we accounted for detection bias due to differential screening with fetal echocardiography by excluding children undergoing at least one fetal echocardiography. Furthermore, we carefully considered the potential for unmeasured

confounding by performing relevant sensitivity analyses. In manuscript #6, we used Bayesian latent class models to account for imperfect autism spectrum disorders case ascertainment in administrative data.

Moreover, in all studies included in this thesis, we used appropriate statistical methods (such as Huber-White correction, GEE, and random effect models) to account for correlation in reproductive outcomes.

The methodology developed through our work on CHD and autism spectrum disorders will help the conduct of future research assessing additional major illnesses in offspring of women with SLE, such as the risk of hematological malignancies and autoimmune diseases. In addition, later research efforts could help address some limitations inherent to the OSLER cohort, such as limited power to fully investigate the potential role of in utero medication exposure on the risk of CHD and autism spectrum disorders in SLE offspring, as well as the lack of maternal serological information (e.g. maternal anti-SSA/Ro antibodies). For example, a future project could consist of the creation of a population-based pan-Canadian cohort of children born to women with systemic autoimmune rheumatic diseases (SARDs, which include SLE, rheumatoid arthritis, systemic sclerosis, primary Sjögren's disease, inflammatory myopathies, and vasculitis). This pan-Canadian cohort would not only provide the appropriate sample size to investigate the potential role of in utero drug exposure on CHD and autism spectrum disorders in SLE offspring, but would also enable us to assess obstetrical complications and long-term outcomes in other SARDs, such as rheumatoid arthritis and systemic sclerosis, which are less prevalent than SLE in women of childbearing years. Furthermore, we could obtain data from other data sources; one example may be the Clinical Practice Research Datalink

(CPRD) in the United Kingdom, which provides maternal serological information (e.g. maternal anti-Ro antibodies).

In summary, this thesis research provides novel information on live birth rates in SLE and outcomes in offspring born to affected mothers, which should help physicians provide adequate counseling to women with SLE contemplating pregnancy, as well as direct future research efforts.

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Appendix A. List of tables

Appendix B. List of abbreviations

ACR	American College of Rheumatology
ADHD	Attention deficit hyperactivity disorder
aPL	Antiphospholipid antibodies
ASD	Autism spectrum disorders
CAI	"Commission d'accès à l'information du Québec"
CHD	Congenital heart defects
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CNS	Central nervous system
CrI	Credible interval
CTD	Connective tissue disease
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
EUROCAT	European Surveillance of Congenital Anomalies
FRQS	"Fonds de recherche du Québec - Santé"
GEE	Generalized estimating equations
GnRH	Gonadotropin releasing hormone
HCQ	Hydroxychloroquine
ICD	International classification of diseases
IgG	Immunoglobulin G
IL-6	Interleukin-6
ISQ	"Institut de la statistique du Québec"
IVF	In vitro fertilization
LBW	Low birth weight
MAR	Missing at random
MCAR	Missing completely at random
MED-ECHO	"Maintien et exploitation des données pour la clientèle hospitalière"
MICE	Multivariate imputation by chained equations
MI-GEE	Multiple imputation generalized estimating equations
NMDAR	N-methyl-D-aspartate receptor
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OSLER	Offspring of Systemic Lupus Erythematosus mothers Registry
QIC	Quasi-Akaike information criterion
RA	Rheumatoid arthritis
RAMQ	"Régie de l'assurance maladie du Québec"
RAMQ-Rx	RAMQ prescription database
RR	Relative rate
SD	Standard deviation
SDI	SLICC damage index
SGA	Small for gestational age
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
SLEDAI-2K	SLE disease activity index - 2000
SLICC	Systemic Lupus International Collaborating Clinics

SSc	Systemic sclerosis
TGF-beta	Transforming growth factor - beta
UK	United Kingdom
US	United States
USA	United States of America
VSD	Ventricular septal defect

Appendix C. Description of study populations

C.1. Systemic Lupus International Collaborating Clinics (SLICC) Prospective Inception Cohort Subsample

In manuscript #3, we studied women with SLE from centers participating in the SLICC Prospective Inception Cohort Study of SLE and agreeing to share data for the present study. At the time of our study, 26 SLICC centers from 11 countries in North America, Europe, and Asia were involved in the inception cohort (including overall 1124 SLE women), among which 11 centers participated in our study (from Canada, United Kingdom, United States, and Sweden). The SLICC inception cohort enrolled patients within 15 months of meeting ≥ 4 American College of Rheumatolgy (ACR) classification criteria for SLE from 2000 to 2013.[212] We only included in our study women fulfilling the SLE ACR criteria before the age of 50, and enrolled in the SLICC inception cohort between 2000 and 2007, representing 339 women. Demographic and clinical data, including number of children and age at first birth (although not dates of subsequent births), are prospectively collected annually using a standardized questionnaire, filled by a SLICC investigator. The initial goal of the SLICC inception cohort, formerly called the SLICC registry for atherosclerosis (SLICC-RAS), was to study cardiovascular outcomes in SLE patients and identify potential predictors.[213] Howevr, the wealth of information collected through the SLICC-RAS has been used for several other studies investigating other outcomes, such as malignancies.[214] In our study, we assessed the number of children born to women with SLE from the age of 15 years up to the age of 50 years, death or the oldest age attained at the last follow-up visit, if the subject was aged <49 years.

C.2. Quebec population-based SLE cohort

The cohort of incident SLE women studied in manuscript #4 was identified by using Quebec MED-ECHO and RAMQ physician billing databases, from 1994/01/01 to 2003/12/31. MED-ECHO is the administrative database collecting information on all hospitalizations in Quebec since 1987, and provides, for each hospitalization, a primary discharge diagnosis and up to 15 non-primary diagnoses, captured as International Classification of Diseases (ICD)-9 codes (and since 2006, ICD-10 codes). RAMQ billing database records one physician-assigned diagnosis, based on ICD-9 codes, for each physician encounter. Incident SLE cases were defined as women with ≥1 hospitalization with either a primary or secondary diagnosis of SLE, or ≥2 physicians' claims for SLE within any 2-month-to-2-year period, with no prior diagnosis of SLE in the 5 years preceding the interval. To assess women diagnosed with SLE during their reproductive period, only women aged 15-35 years on 1994/01/01 were included, representing 1334 SLE women. We determined the number of live births during the interval as defined by diagnostic and procedure codes for delivery in the MED-ECHO and RAMQ physician databases, respectively, up to the age of 45 years, death or or the oldest age attained at the end of the study period.

C.3. Offspring of SLE mothers Registry (OSLER)

OSLER is a population-based cohort of 719 children born to mothers with SLE, matched to 8493 control children. and served as the study population in manuscripts #5 and #6. To create this large cohort, we identified all women with SLE who had at least one hospitalization for a delivery (including both stillbirths and live births) between 01/1989 and 12/2009, using data from the Quebec MED-ECHO and RAMQ physician billing databases.

Women were identified as SLE cases (based on a validated definition,[18] using ICD-9 code 710.0 or ICD-10 code M32) if they had any of the following: 1) at least one 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) at least 2 physician visits with a diagnosis of SLE, occurring 2 months to 2 years apart, prior to the delivery. From these databases, a general population control group was composed of women matched at least 4:1 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, which is present in every child's file in the RAMQ and MED-ECHO databases, and where it remains through childhood, leading to very few linkage failures (< 2%). Those children born live were the basis of the OSLER cohort for outcome ascertainment, the exposed group consisting of children born to women with SLE, and the control group consisting of children born to women without SLE. Stillbirths were not included since a substantial proportion of births labeled as stillbirths in Quebec result from pregnancy termination, for which no information for our outcomes of interest is recorded (neither for SLE mothers, nor controls).[190]

The cohort of children described above was linked to the MED-ECHO and RAMQ databases to determine hospitalizations and all diagnoses occurring throughout the study interval of these offspring. This study interval spanned from birth to the first of the following: end of eligibility for RAMQ coverage (i.e. migration from Quebec), event of interest (e.g. CHD, autism spectrum diosrders), a pre-defined age (12 months for CHD and 18 years for autism spectrum disorders), death, or end of study (i.e. December 31st 2009).

Appendix D. Reprints of published manuscripts

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REVIEW ARTICLE

Systemic Lupus Erythematosus in Women: Impact on Family Size

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that often affects women in their reproductive years. At diagnosis, these women are faced with a life-long illness that may have considerable impact not only on their physical health, but also on their existing family and/or reproductive potential. With recent advances in the management of this condition, it is hoped that good disease control can be achieved in the majority of cases, and therefore most of these women are not advised to avoid pregnancy. However, multiple disease-related factors may still affect the number of children born to women with SLE.

The influence of SLE on reproduction and family size has been investigated (1–3). A study by Hardy et al demonstrated that white women with SLE appeared less likely to have more than 2 children compared with a control group (odds ratio [OR] 0.56, 95% confidence interval [95% CI] 0.31–1.03) (1). In a population-based study of women with rheumatic diseases, a lower number of births and a reduced period of reproduction were observed in women with connective tissue diseases, including SLE, compared with healthy controls (mean, 95% CI 1.7, 1.5–1.9 versus 2.2, 2.1–2.3) (2). The interpregnancy interval was longer and the proportion of women achieving a subsequent pregnancy was reduced in women with connective tissue diseases. However, these findings may not be specific for patients with SLE.

Similar data were shown in a study of women with rheumatoid arthritis (RA) (4). Women diagnosed with RA prior to the birth of their first child had fewer pregnancies and children, and 20% reported that RA had affected their decision to have children or their decision about family size. The disease aspects most commonly reported to affect childbearing decisions were concerns about being able to care for a child, medication issues (including fear that medication would affect the fetus and concerns about stopping medication), as well as fears that their own children may eventually develop the disease.

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Childbearing Decision

In women with SLE, several characteristics of the disease should be considered before planning pregnancy, and these characteristics may also impact a woman's capacity and decision to have children. Although still controversial, there is a reported probable increased risk of disease flare during pregnancy and in the postpartum period. Although several small studies found no significant increase in SLE activity during pregnancy (5–8), more recent studies have found a 2- to 3-fold increase in SLE activity during pregnancy (9–12). Based on these studies, 35–70% of all pregnancies will have measurable disease activity, with most studies showing the risk to be 40–50% (7,8,10,11). The risk for a moderate to severe flare is lower and ranges from 15–30% (13–15). Recent data have demonstrated the absence of fetal toxicity with the use of hydroxychloroquine (HCQ) in pregnancy (16,17). Because HCQ discontinuation is associated with an increased risk of disease flare in pregnant and nonpregnant patients (16–18), and because HCQ is no longer contraindicated during pregnancy (19), it is likely that the risk of disease flare in pregnancy will be reduced. Nevertheless, disease exacerbation can occur at any time during pregnancy, as well as several months after delivery. Women with no or mild disease activity in the 6 months preceding pregnancy are less likely to experience disease exacerbation (20). For this reason, it is generally recommended that women have stable disease for 6 months before conceiving. This recom-

mendation could potentially delay motherhood or increase the interval between pregnancies in some women.

Pregnant women with SLE are at increased risk of miscarriage or stillbirth. Approximately 20% of pregnancies in women with SLE will end in a miscarriage (a pregnancy loss at <20 weeks gestation), as compared with 9% in the general population (1,21). Some studies have demonstrated that this risk was present even before SLE diagnosis, with almost a 2-fold increase compared with controls (OR 1.99, 95% CI 1.28–3.10) (1). The risk of stillbirth (a pregnancy loss at >20 weeks gestation) has also been shown to be elevated in several studies, with an ~3-fold increase compared with the general population (9). The two most important risk factors for pregnancy loss are increased SLE activity and antiphospholipid syndrome (21). Obviously, miscarriages and stillbirths may directly contribute to a reduction in family size.

In addition, SLE is associated with an increased risk of maternal complications during pregnancy, including pregnancy-induced hypertension, preeclampsia, and thromboembolic events (20). In the general population, preeclampsia complicates 5–8% of pregnancies (20). However, the rate of preeclampsia ranges from 13–35% in women with SLE (15,21–23). Preeclampsia can lead to significant complications, including preterm birth, stroke, and even death (20).

Furthermore, certain drugs used to treat SLE manifestations, such as methotrexate and cyclophosphamide, are contraindicated during pregnancy because of potential fetal harm (24). Recently, mycophenolate mofetil, a relatively recent addition to the treatment of SLE, has been shown to be potentially associated with a specific pattern of congenital malformations, which notably includes cleft lip and palate, microtia, micrognathia, and hypertelorism (25–28). These medications must be discontinued or switched to safer ones in prevision of conception, and this requires planning under supervision of a health care professional. Dependence on a medication in order to maintain disease control may delay pregnancy in some patients.

Moreover, future mothers might be worried that their children may be affected by SLE, even if this risk is small. There is evidence that SLE occurrence is increased in the offspring of patients with SLE, and prevalence has been estimated at ~4% in the children of parents with SLE (29). Other studies have shown that up to 12% of SLE patients had first-degree relatives with SLE or other connective tissue diseases (30). Other autoimmune diseases, such as autoimmune thyroid disease, are also more common in first-degree relatives, including children of patients with SLE (31). There is some evidence that the disease onset may be earlier in the child than in the affected mother (31), representing a general phenomenon reported in genetically-transmitted diseases.

As a result of drug exposure, maternal disease activity, or complications, the baby may be born prematurely, have low birth weight, or intrauterine growth retardation (IUGR). Estimates of the number of pregnancies in women with SLE that end in premature delivery (delivery before 37 weeks gestation) have ranged widely, generally between 10–50% (20); higher estimates may relate to sicker patients seen in tertiary care centers. In a population-based study of 555 SLE deliveries in the US, 21% were preterm, which corresponded to an approximately 6-fold higher rate compared with healthy women (32). In general, premature babies have an increased risk of respiratory complications, infections, developmental abnormalities (especially neurologic), and death in the neonatal period (33).

On average, ~10% of all babies born of mothers with SLE are small for their gestational age (weight below the 10th percentile for gestational age) comparable with what would be expected in the general population (20). However, some cohorts report increased rates as high as 35% (10,15,21); the higher figures may again relate to sicker SLE patients from tertiary care centers. In the general population, there is some evidence that low birth-weight or IUGR babies may be at risk of developing Type 1 diabetes mellitus (34,35), early-onset hypertension (for example, in adolescence) (36), and premature coronary artery disease (37). Some studies have suggested there is an increased risk of learning disabilities (incidence of 20–30%) in children of women with SLE, particularly in boys (38–41). However, most of these studies relied on self-report, which could have biased the estimates. Only limited data are available on the long-term outcomes of children born to mothers with SLE.

Faced with the potential risks of disease flare and/or adverse maternal and fetal outcomes, and considering the additional physical, social, and emotional demands related to the management of SLE, some women may choose not to have children. In a study assessing social functioning in 114 women with SLE, 49% had children, 32% planned to have a child or another child, 18% planned no children, and 1% were undecided. SLE was viewed as a barrier to childbearing by 27% (30). Common concerns included worries that pregnancy might exacerbate the disease, that medications or the disease might harm the fetus, and that the disease might interfere with childcare. In another study addressing disease impact on family planning in 40 women having children after SLE diagnosis, 45% of women reported anxiety about pregnancy, in most cases related to the fear of transmitting the disease to their offspring (38). In addition, 23% reported that SLE interfered with their ability to attend to their family.

Personal Relationships and Sexuality

Women with SLE have impaired sexual function (42). The disease can affect sexual function in different ways. Physical problems (i.e., chronic pain and fatigue) and emotional problems (i.e., low self-esteem and depression) can decrease sexual interest and reduce intercourse frequency. Disturbances of hormonal status by corticosteroid treatment and disease activity can reduce libido and interfere with successful reproduction (43). Partnership difficulties arising from disease-related stress can also contribute to a less active sexual life (44). In a study by Boomsma et al (45), 20% of SLE patients thought that their illness had driven their family apart or worsened their relationship with their partner.

The impact of SLE on sexuality is not necessarily addressed by health care professionals, and is not part of questionnaires used routinely to assess physical function

or quality of life in SLE populations (43). A recently validated disease-specific health-related quality of life instrument, the LupusQol, assessed intimate relationships, and patients who were asked for feedback thought it was an important aspect of the questionnaire (46). Patients and health care professionals may be reluctant to discuss the issue, even when there is marked impairment of sexual function (43). This miscommunication was highlighted in a study of 74 RA patients where only one patient reported being asked if the disease had caused any sexual problems (47). Most sexually active women with SLE have problems with sexual function when acutely ill (30). Disease intrusiveness on sexuality does not seem to differ between males and females in subjects with RA, but this has not been assessed in SLE patients (48). Understanding and support during SLE disease exacerbations has been cited as the most important factor leading to an adequate sexual lifestyle adjustment (30). Therefore, health care providers should be aware of how SLE can interfere with the relationships of their patients, and affect sexuality. The health care provider can also help by encouraging communication between the patient and significant others, and by providing information on how the disease and its therapy can affect a patient's sexual life. Consultation with specialists may be helpful; a gynecology opinion may be helpful for physical factors, and psychotherapy may be useful for psychological issues.

Fertility

In women with SLE, fertility might be impaired due to associated autoimmune anomalies, therapies (i.e., cyclophosphamide), and hormonal dysfunction (i.e., transient amenorrhea). Antiphospholipid antibodies (aPL) are known to be associated with pregnancy losses (49). Murine studies suggest that aPL induce pregnancy loss through disruption of placental circulation and could also interfere with implantation of the embryo (50). However, the role of aPL in infertility and in vitro fertilization failure is still controversial in humans. Several retrospective studies have shown a positive association between aPL and in vitro fertilization failure, although prospective studies, the largest study assessing 793 women, have not confirmed this (51,52). The underlying mechanisms by which aPL impair reproductive function are still obscure.

Although it is unclear if the disease itself is associated with infertility, some drugs used in its treatment might cause infertility that is either reversible (i.e., nonsteroidal antiinflammatory drugs [NSAIDs]) or potentially irreversible (i.e., cyclophosphamide) (43). Prostaglandins, inhibited by NSAIDs, are involved in ovulation and implantation. Several case reports and small series of women with rheumatic diseases have described transient infertility following treatment with NSAIDs, including indomethacin, diclofenac, and naproxen (53,54). Animal and human studies have shown that NSAIDs can inhibit rupture of the luteinized follicle, which can cause infertility (43,55). However, the magnitude of this adverse effect has not been established at the present time.

Premature ovarian failure has been observed after treatment with alkylating agents such as cyclophosphamide. The gonadal toxicity of cyclophosphamide is related to cumulative dose, administration route, and age at treatment onset (56). Women younger than 26 years are less likely to develop ovarian failure than those who started treatment at a later age (57). The frequency of premature ovarian failure due to cyclophosphamide varies from 11–59% (56). A recent study showed that treatment with synthetic gonadotropin-releasing hormone (GRH) while receiving cyclophosphamide significantly reduced the risk of premature ovarian failure. Only 5% of the GRH-treated group developed ovarian failure compared with 30% in the control group (58).

Moreover, menstrual irregularities and anovulatory cycles have been reported in patients with active disease and in those treated with high-dose corticosteroids (59). End-stage renal failure secondary to lupus nephritis can also result in amenorrhea (60).

Although fertility might be impaired in several ways, there is a general notion that SLE does not diminish fertility in affected women. However, this aspect of reproduction in women with SLE has never been adequately measured. Most authors cite a 1974 study by Fraga et al (3) that reported a fertility rate in women with SLE that was comparable with an age-matched control group of healthy women. However, the fertility rate was calculated using the number of pregnancies in women who had at least 1 pregnancy. This overestimated the number of pregnancies per woman with a diagnosis of SLE, because those who did not achieve any pregnancy were excluded. In this study, a total of 79 women with SLE and 80 healthy subjects with a mean (range) age of 33.1 (17–62) years were evaluated. There were a total of 183 pregnancies among 53 patients before the clinical diagnosis of SLE, which resulted in 42 spontaneous abortions and 141 live births. In the remaining 26 SLE patients, no pregnancy occurred. Forty-two pregnancies occurred in 20 patients after the onset of SLE, and 33 women did not become pregnant again. Of the 42 pregnancies, 17 ended in spontaneous abortions and 25 in live births. In 24% of the 26 women who did not have further pregnancies, the only associated factor appeared to be disease activity. In the control group, 288 pregnancies occurred in 80 women, resulting in 252 live births. In fact, these results raise the possibility that fertility rate and birth rate might be reduced in women with SLE, particularly after diagnosis.

One difficulty in assessing fertility in women with SLE is the lack of consensus on the definition and measurement of fertility. Demographic studies generally define fertility rate as the number of live births per 1,000 women of reproductive years (usually between age 15 and 44 years) in a given year (61). From this rate, a synthetic fecundity index is generally derived in demographic studies to estimate the mean number of children that a woman would have if her fertility rate during her entire life followed the same rate as reported for her population age group (61). These measures are useful for large population studies, but are difficult to apply to the study of women with SLE, in order to allow comparison with population figures.

Some refer to fertility as the absence of infertility, which itself is usually defined as the inability of a couple of

reproductive age to establish a pregnancy within one year by having regular sexual intercourse (62). To date, no study has attempted to measure the prevalence of infertility in women with SLE by using this widely accepted definition. There is also no information on the time to conception in SLE. This represents an important deficiency, as these data are necessary to counsel women with SLE regarding their childbearing capacities.

Conclusion

Although most women with SLE would like to have children (63), some studies have shown a reduction in their family size (1,2). Many factors, both physical and psychosocial, may influence childbearing decisions and the capacity to have children. The relative importance of these factors may vary according to disease activity, damage, and/or treatment. More studies are needed to evaluate how SLE affects reproduction, particularly the extent to which fertility is altered in women with SLE.

AUTHOR CONTRIBUTIONS

Dr. Vinet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Vinet, Pineau, Gordon, Clarke, Bernatsky.

Acquisition of data. Vinet, Gordon.

Analysis and interpretation of data. Vinet, Pineau, Gordon, Clarke, Bernatsky.

Manuscript preparation. Vinet, Pineau, Gordon, Clarke, Bernatsky.

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REVIEW

Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus

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Children born to women with systemic lupus erythematosus seem to have a potentially increased risk of neurodevelopmental disorders compared to children born to healthy women. Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for neurodevelopmental disorders. Interestingly, women with systemic lupus erythematosus display high levels of autoantibodies and cytokines, which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring. Furthermore, subjects with systemic lupus erythematosus and neurodevelopmental disorders share a common genetic predisposition, which could impair the fetal immune response to in utero immunologic insults. Moreover, systemic lupus erythematosus pregnancies are at increased risk of adverse obstetrical outcomes and medication exposures, which have been implicated as potential risk factors for neurodevelopmental disorders. In this article, we review the current state of knowledge on neurodevelopmental disorders and their potential determinants in systemic lupus erythematosus offspring. *Lupus* (2014) **23,** 1099–1104.

Key words: Systemic lupus erythematosus; neurodevelopmental disorders; pregnancy

Introduction

In North America, the prevalence of neurodevelopmental disorders, such as autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD), has reached epidemic levels, affecting approximately 10% of school-age children.[1,2] Systemic lupus erythematosus (SLE) is a multi-systemic disease that predominantly affects women during their childbearing years. Children born to women with SLE seem to have a potentially increased risk of neurodevelopmental disorders compared to children born to healthy women.[3–8] Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for neurodevelopmental disorders.[9] Interestingly, women with SLE display high levels of autoantibodies (e.g. anti-N-methyl-D-aspartate receptor (NMDAR) antibodies) and cytokines (e.g. interleukin-6 (IL-6)), which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring.[10,11] Furthermore, subjects with SLE and neurodevelopmental disorders share a common genetic predisposition to the C4B null allele, which could impair the fetal immune response to in utero immunologic insults.[12–14] Moreover, SLE pregnancies are at increased risk of adverse obstetrical outcomes, such as prematurity and low birth weight (LBW), and medication exposures, such as anticonvulsants, which have been implicated as potential risk factors for ASD and ADHD.[15–17] In this article, we review the current state of knowledge on neurodevelopmental disorders and their potential determinants in SLE offspring.

Overview of ASD and ADHD

ASD are now one of the most common neurodevelopmental disorders, with a prevalence ranging from one of 68 to one of 500 children.[2,18] ASD are a group of biologically based

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neurodevelopmental disorders, characterized by onset before the age of 3 years, and impairment in three major domains: socialization, communication, and behavior.[18] ASD are diagnosed clinically and include: autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified.[18]

ADHD prevalence in school-age children is approximately 8%–10% percent, making it one of the most common disorders of childhood.[1] ADHD is a neurodevelopmental disorder that manifests in early childhood with symptoms of hyperactivity, impulsivity, and/or inattention. ADHD symptoms affect cognitive, behavioral, emotional, and social functioning, and it is the persistence and functional complications of the behavioral symptoms that lead to a diagnosis of ADHD.[19] Notably, to meet criteria for ADHD based on the *Diagnostic and statistical manual of mental disorders, 4th ed.* (DSM-IV), symptoms must be present before the age of 7 years.[19]

Multiple inter-related factors potentially play an etiologic role in neurodevelopmental disorders. Increasing evidence supports a strong genetic contribution in the development of ASD and ADHD.[20] Neuroimaging and autopsy studies in neurodevelopmental disorders suggest that structural brain anomalies are implicated, such as prefrontal cortical volume disparities and hypofunction (present both in ASD and ADHD).[21,22] Though the literature shows conflicting results, perinatal factors including preterm birth, LBW, and in utero exposure to maternal smoking, as well as advanced parental age (both paternal and maternal) and maternal obesity, have been associated with an increased risk of neurodevelopmental disorders in offspring.[15,16,18,19,23]

Neurodevelopmental disorders in offspring of mothers with SLE

Some epidemiological data suggest that children born to women with SLE may have an increased risk of neurodevelopmental disorders compared to children born to healthy women. However, the evidence is extremely limited, as only a handful of small observational studies have assessed this issue.

Several retrospective studies suggest that children, more particularly sons, of mothers with SLE are at increased risk (up to 25%–45%) for learning disabilities, such as dyslexia.[3,4,6] In a small retrospective study using parental-report, the prevalence of learning problems due to inattention and hyperactivity in offspring of SLE mothers was more than twice that reported for controls.[4] Recently, a prospective study assessed the neurodevelopment of 57 children born to mothers with SLE and 49 controls using standardized tests.[7] Offspring of SLE mothers had more than a three-fold increase in anomalies related to learning and memory, as well as behavior.

Moreover, autoantibodies commonly found in SLE patients have been associated with an increased risk of neurodevelopmental disorders.[24–26] Notably, in a small cohort study of children born to mothers with anti-Ro antibodies, investigators have shown that exposure to anti-Ro antibodies (present in 30%–50% of SLE patients) is associated with a high parent-reported prevalence of ADHD, present in up to 24% (eight of 33) of exposed children.[24] In addition, in utero exposure to antiphospholipid (aPL) antibodies (found in up to 30% of subjects with SLE) has been linked to a high prevalence of learning disabilities (four of 17 exposed children) and ASD (three of 45 exposed children) in two small cohort studies of children born to aPL antibodies-positive mothers.[26,27] In a recent retrospective cohort study of 60 SLE offspring, in utero exposure to azathioprine conferred more than a six-fold increased risk of having special educational needs (used as a proxy for developmental delays), when adjusting for disease severity and obstetrical complications.[8]

Although previous studies support the hypothesis of an increased risk of neurodevelopmental disorders in offspring of SLE mothers, these studies were marked by important methodological limitations: All had limited sample size, only one controlled for obstetrical complications and medication exposures, and most used parental-report, did not include a control group, and/or were retrospective in nature.

Case-control studies of SLE in mothers of children with neurodevelopmental disorders

In addition to cohort evidence of an increased risk of neurodevelopmental disorders in offspring of mothers with SLE, numerous case-control studies have suggested an increased prevalence of SLE and other autoimmune diseases in mothers of children affected with neurodevelopmental disorders.[28–30] In a case-control study of 61 children with ASD and 46 healthy controls, affected children had more than an eight-fold increase in the odds of having a mother with an autoimmune disorder (by her self-report) than unaffected children.[30] Among the most common maternal autoimmune disorders, SLE was

observed in 13% of children with ASD, versus 4% of healthy controls.

A large population-based study using administrative data showed similar results, although the estimates were more conservative.[28] In this study, children with ASD were more likely than unaffected children to have a mother diagnosed with an autoimmune rheumatic disease such as SLE (relative risk (RR) 1.56, 95% confidence interval (CI) 1.08, 2.17), while the likelihood of having a father with these diseases did not differ. This suggests that the association between SLE and neurodevelopmental disorders might be influenced by a prenatal exposure to maternal antibodies and/or fetal environment during gestation.

Role of maternal antibodies in neurodevelopmental disorders

Currently, in utero exposure to maternal immunoglobulin G (IgG) antibodies is attracting great attention as an important environmental risk factor for neurodevelopmental disorders. It is well known that maternal IgG antibodies begin to cross the placenta at the second trimester of pregnancy, reaching circulating levels in the newborn that exceed maternal levels, due to active transport across the placenta.[9] In the presence of maternal autoimmunity, autoantibodies also cross the placenta and can interfere with fetal development. Although offending maternal autoantibodies are cleared from the child's circulation within the first six months of life, it is known that autoantibody-mediated injury in utero can result in long-term damage to organs (e.g. congenital heart block in neonatal lupus).[31]

Though the blood-brain barrier blocks IgG entry into the adult central nervous system (CNS), in the fetus, the immature blood-brain barrier allows IgG access to the developing brain.[9] Genetic predisposition may increase the susceptibility to neurodevelopmental disorders in children exposed in utero to offending maternal IgG.[32]

Antibodies directed against fetal brain proteins (proteins yet to be identified) have been observed in 10%–12% of mothers of children with ASD.[9] This antibody reactivity has been shown to be *absent* in mothers of normally developing children. Also, human maternal fetal brain-reactive antibodies from mothers of children with ASD, when administered to pregnant mice, cause behavioral alterations in the offspring, including hyperactivity and decreased social interaction.[33] In this mouse model, an increased number of microglial cells were observed in the brain of exposed offspring, suggesting that these brain-reactive antibodies may mediate their effects through inflammatory changes.[33]

Furthermore, studies have demonstrated a significant association between maternal fetal brain-reactive antibodies and specific patterns of ASD.[9] For example, children with ASD whose mothers harbored fetal brain-reactive antibodies were more likely to have a regressive form of autism than unexposed children.[34] In addition, Diamond et al. recently showed that 53% of mothers of an ASD child with fetal brain-reactive antibodies also exhibited antinuclear autoantibodies compared with 13% of ASD mothers without fetal brain-reactive antibodies and 15% of control women.[35] They also observed an increased prevalence of autoimmune diseases, especially SLE, in ASD mothers with fetal brain-reactive antibodies. These findings suggest that a subset of ASD might be related to in utero maternal antibody exposure, a mechanism potentially involved in patients born to SLE mothers.

Autoantibodies and cytokines in SLE potentially affecting fetal neurodevelopment

New experimental data have further substantiated a potential link between in utero exposure to SLE and neurodevelopmental disorders. A subset of anti-double-stranded DNA (anti-dsDNA) antibodies, the anti-NMDAR antibodies, present in up to 60% of women with SLE, has been shown in a mouse model to cross the placenta, induce fetal brain neuronal apoptosis by binding NMDAR, and cause cognitive impairments in offspring, preferentially in males.[10,36] Affected offspring displayed smaller-sized neocortical neurons and neuronal migration defects, findings observed in histological studies of humans affected with learning disabilities and ADHD.[21]

It is noteworthy that pregnant mice exposed to anti-NMDAR antibodies had a marked preferential loss of female fetuses, resulting in an increased male-to-female ratio in their offspring compared to the offspring of unexposed mice.[10] Interestingly, we have recently demonstrated that mothers with SLE had substantially increased odds of having male offspring than mothers without SLE (odds ratio (OR) 1.18, 95% CI 1.01, 1.38) using our large population-based cohort.[37] This finding mirrors experimental data and parallels the male predominance seen in neurodevelopmental disorders.

Of particular interest, in human studies, mutations in genes leading to reduced NMDAR function have been associated with ASD and

ADHD.[38–42] In addition, the NMDAR partial agonist d-cycloserine has been shown to restore NMDAR function and efficaciously treat the core symptom of social withdrawal in children with ASD.[43]

In addition to anti-NMDAR antibodies, other autoantibodies found in SLE could potentially alter fetal brain development. aPL antibodies, present in 30% of women with SLE, are known to cross the placenta and have been found at high levels in the serum of exposed neonates.[25] These antibodies can bind CNS cells and, in experimental models, prolonged exposure to aPL antibodies induces hyperactive behavior and neurological dysfunction in mice.[44,45] Thus, these autoantibodies might also be implicated in inducing neurodevelopmental disorders in children born to women with SLE.

As well as maternal antibodies, maternal cytokines may reach the fetal circulation.[20] The maternal cytokine milieu might constitute an important environmental risk factor for neurodevelopmental disorders. Notably, IL-6 is known for its primordial role in brain development.[11] IL-6 administration in pregnant mice caused substantial behavioral and social deficits in the offspring, while co-administration with an anti-IL-6 antibody prevented these deficits.[11]

IL-6 is involved in autoantibody production in SLE, and affected patients have markedly elevated IL-6 blood levels.[46] Thus, in SLE pregnancies, IL-6 could possibly have a direct effect on the fetal brain or enhance the production of maternal fetal brain-reactive antibodies, which could cross-react with the fetal brain, leading to neurodevelopmental disorders in exposed fetuses.

Genes associated with SLE and neurodevelopmental disorders

Genes long implicated in autoimmune disorders, such as SLE, are significantly more prevalent in subjects with ASD and ADHD.[20] One of these genes is the C4B null allele, which is strongly associated with SLE. Depending on the population studied, SLE subjects are up to six times more likely than controls to harbor the C4B null allele.[12] Of particular interest, the C4B null allele is four times more common in individuals with ASD compared with controls.[13] Moreover, the C4B null allele has also been associated with ADHD, being present in 57% of affected subjects compared to 20% of controls.[14] As presence of the C4B null allele leads to partial C4B deficiency, and since the complement system is involved in brain tissue remodeling and repair, alterations in C4B levels could alter the fetal immune response to in utero immunologic insults, resulting in pathologic changes.[14]

Drugs, obstetrical complications in SLE and risk of neurodevelopmental disorders

SLE pregnancies are at increased risk of adverse obstetrical outcomes, such as prematurity and LBW, which are potential risk factors for ASD and ADHD. Approximately 25% of lupus pregnancies end in preterm birth and 15% of the neonates are LBW.[47–49] Observational studies report a 1.5- to three-fold increase in neurodevelopmental disorders in children born preterm or LBW versus controls.[15,16] Thus, obstetrical complications in women with SLE may also increase neurodevelopmental disorders in offspring.

In the general population, very few data exist on drug exposures during pregnancy and neurodevelopmental disorders in offspring. Anticonvulsant use during pregnancy, in particular valproic acid, has been associated with an increased risk of ASD in children from the general population.[17] Women with SLE are possibly more likely than unaffected women to be exposed (inadvertently or not) to certain drugs during pregnancy, including anticonvulsants (used to control SLE-related seizures or other neurological manifestations). Moreover, as potentially suggested in the study by Somers et al.,[8] in utero exposure to immunosuppressives, such as azathioprine, might mediate the risk of neurodevelopmental disorders in children of mothers with SLE. However, more studies are needed to confirm this potential drug effect, as it might also represent confounding by disease severity. In addition, uncontrolled disease activity as a consequence of drug avoidance during pregnancy might be associated with an even greater risk of neurodevelopmental disorders than in utero drug exposure itself.

To summarize, SLE is an important autoimmune disease and recent evidence suggests an increased risk of neurodevelopmental disorders in children born to affected women. The offspring of SLE mothers face several potential risk factors for neurodevelopmental disorders, including in utero exposure to maternal antibodies and cytokines, obstetrical complications, and drugs. In addition, both SLE and neurodevelopmental disorders share a common genetic predisposition. Thus, it is imperative to further study neurodevelopmental disorders and their determinants in the offspring of SLE mothers.

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BRIEF REPORT

Decreased Live Births in Women With Systemic Lupus Erythematosus

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Objective. **Multiple disease-related factors may limit the number of children born to women with systemic lupus erythematosus (SLE). We calculated live births in women with SLE and compared this with general population rates.**

Methods. **We studied women with SLE from a subset of centers participating in the Systemic Lupus International Collaborating Clinics Prospective Inception Cohort Study of SLE. Women diagnosed as having SLE before age 50 years were included. Using age, calendar-period, and country-specific general population birth rates, we calculated the standardized incidence ratio (SIR) of observed to expected live births. We also performed a multivariate analysis with the SIR as the dependent variable to explore potential predictors of live births.**

Results. **A total of 339 women with SLE were studied. The number of live births over the interval (n = 313) was substantially below that which would be expected (n = 479; SIR 0.65, 95% confidence interval [95% CI] 0.58–0.73). In the multivariate analyses, black race/ethnicity (SIR 1.47, 95% CI 1.08–2.00) and being married or living common-law (SIR 2.04, 95% CI 1.52–2.74) were associated with increased live births (relative to what would be expected). There were trends for fewer live births in women exposed to cyclophosphamide (SIR 0.88, 95% CI 0.56–1.38) and in those with high disease activity (mean SLE Disease Activity Index 2000 update score ≥5; SIR 0.82, 95% CI 0.54–1.25).**

Conclusion. **Overall, we found that women with SLE have fewer live births compared with the general population. Marital status, race/ethnicity, and possibly clinical factors may mediate this effect.**

Introduction

Multiple disease-related factors may limit the number of children born to women with systemic lupus erythematosus (SLE). These factors potentially include decreased fertility, adverse pregnancy outcomes (e.g., miscarriages or stillbirths), relative contraindications to pregnancy (e.g., high disease activity or dependence on a teratogenic medication), impaired sexual function and/or personal relationships, or a deliberate decision to limit family size (1).

Many women with SLE ask if the disease will affect their capacity to have children, but studies assessing the impact of SLE on family size are scant. One case–control study suggested that white women with SLE appeared less likely to have >2 children compared with healthy controls, but

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the results were not precise (odds ratio 0.56, 95% confidence interval [95% CI] 0.31–1.03) (2). In a population-based study of women with rheumatic diseases, a lower number of births was observed in women with connective tissue diseases, including SLE, compared with controls (mean 1.7; 95% CI 1.5–1.9 versus mean 2.2; 95% CI 2.1–2.3) (3). The interpregnancy interval was longer, and the proportion of women achieving a subsequent pregnancy was reduced in women with connective tissue diseases. Although these studies suggest a potential negative impact of SLE on family size, they are limited; both studies were small and only one study specifically evaluated women with SLE. In addition, neither restricted the analysis to women diagnosed as having SLE before or during their reproductive period, nor adjusted for the reproductive period duration.

Therefore, our primary objective was to calculate the number of live births in a cohort of women diagnosed as having SLE during their reproductive years, and to compare this with general population rates. We also explored potential demographic, social, and clinical factors that might be associated with lower birth rates in women with SLE.

Subjects and Methods

We studied women with SLE from centers participating in the Systemic Lupus International Collaborating Clinics (SLICC) Prospective Inception Cohort Study of SLE and agreeing to share data for the present study. The SLICC Inception Cohort enrolls patients within 15 months of meeting ≥4 American College of Rheumatology classification criteria for SLE (4). Demographic and clinical data, including number of children and age at first birth (although not dates of subsequent births), are prospectively collected using a standardized questionnaire.

We assessed the number of children born to women with SLE, evaluating only women diagnosed as having SLE before the age of 50 years. We determined the number of children born (both before and after the SLE diagnosis) as of the last followup (the observed number of live births) in order to calculate the standardized incidence ratio (SIR). The SIR is the ratio of the observed number of live births in a sample divided by the expected number of live births. We determined the expected number of live births as follows. We summed the years of followup from ages 15–50 years (or the oldest age attained if the subject was age <49 years). We applied age- and country-specific general population birth rates for the relevant calendar periods to these years of followup to obtain the expected number of births for the period of followup. Race-specific birth rates were only available for the US. In sensitivity analyses, we applied these rates to the overall sample to adjust for its racial distribution.

In secondary analyses, we explored potential predictors of live births using multivariate Poisson regressions with the SIR (not itself adjusted for race/ethnicity) as the dependent variable. The potential predictors of live births included in the analyses were race/ethnicity, marital status, age at diagnosis, disease duration, cyclophosphamide exposure (i.e., ever/never exposed), presence of antiphospholipid antibodies (aPL; either lupus anticoagulant, anti–β_2-glycoprotein I, or anticardiolipin antibodies on at least 1 occasion), disease activity (defined by the mean SLE Disease Activity Index 2000 update [SLEDAI-2K] score), and damage (defined by the SLICC Damage Index [SDI] score). Time-dependent variables (including mean SLEDAI-2K and SDI scores) were assessed at the last followup. Since repeated reproductive outcomes are not independent, we applied the Huber-White correction to our multivariate model using all births and performed a sensitivity analysis restricted to first births using parity-adjusted birth rates (i.e., general population rates for first births and comparing live birth rates for first births in women with SLE to the general population) to assess the statistical validity of our multivariate model.

Results

A total of 339 women with SLE from 11 centers were studied. The mean ± SD age at diagnosis was 35.3 ± 13.3 years, and the mean ± SD disease duration at the last visit was 2.7 ± 2.0 years. Most of the women (43%) were from the US, 27% were from Canada, 27% were from the UK, and 3% were from Sweden. The majority of the women (61%) were white and most (42%) were currently married or living common-law.

Regarding reproductive history, the mean ± SD age at menarche was 12.9 ± 1.6 years, and the mean ± SD age at menopause was 45.5 ± 7.9 years. The majority (54%) never had a live birth, with 42% of the women reporting never having been pregnant. The mean ± SD age at first birth was 25.2 ± 6.2 years, and almost all first births (89%) occurred before the SLE diagnosis.

A total of 478 pregnancies were observed from age ≥15 years, up to the subject's age at the last visit (Table 1). Among 293 women for whom complete information on abortions was available, 74% of pregnancies resulted in live births, 20% in spontaneous abortions, and 6% in elective terminations.

Overall, the number of live births over the interval (n = 313) was substantially below that which would be expected (n = 479; SIR 0.65, 95% CI 0.58–0.73) (Table 2). We found almost identical results using race-specific general population birth rates (SIR 0.65, 95% CI 0.58–0.72). The difference between the observed and the expected number of live births over the interval was attenuated when we restricted the analysis to first birth only (SIR 0.92, 95% CI 0.78–1.07).

Multivariate analyses (with the SIR as the dependent variable) were performed with either all births or first births only, yielding similar results (Table 3). In these analyses, the SIR itself was not adjusted for racial differences in national birth rates, but we did include variables for race/ethnicity in our models. Black race/ethnicity (SIR 1.47, 95% CI 1.08–2.00) and being married or living common-law (SIR 2.04, 95% CI 1.52–2.74) were associated with increased live births (relative to what would be expected).

We observed fewer live births in Asian women (SIR 0.50, 95% CI 0.28–0.89). This represents a relative decrease in live births for Asian women diagnosed as having

Table 1. Reproductive events from age 15 years to end of followup*

Events, no.	Gravidity (n = 339)	Parity (n = 339)	Spontaneous abortion (n = 293)	Therapeutic abortion (n = 293)
0	142 (41.9)	184 (54.3)	242 (82.6)	277 (94.5)
1	59 (17.4)	56 (16.5)	37 (12.6)	14 (4.8)
2	58 (17.1)	54 (15.9)	7 (2.4)	1 (0.3)
3	41 (12.1)	33 (9.7)	6 (2.1)	1 (0.3)
4	25 (7.4)	11 (3.2)	1 (0.3)	0 (0)
5	8 (2.4)	1 (0.3)	0 (0)	0 (0)
≥6	6 (1.8)	0 (0)	0 (0)	0 (0)

* Values are the number (percentage) unless otherwise indicated.

SLE, versus the general population, in contrast to women with SLE of other ethnicities. In addition, there were trends for fewer live births in women exposed to cyclophosphamide (SIR 0.88, 95% CI 0.56–1.38) and in those with high disease activity (mean SLEDAI-2K score ≥5; SIR 0.82, 95% CI 0.54–1.25).

We did not definitively establish a decrease in live births independently associated with the presence of aPL (SIR 0.94, 95% CI 0.67–1.33) or disease damage (SDI score ≥2; SIR 0.99, 95% CI 0.65–1.51) when demographic and clinical characteristics were adjusted for.

Discussion

We observed that women diagnosed as having SLE during their reproductive period have substantially decreased live birth rates compared with the general population. This finding persisted after adjusting for race/ethnicity using race-specific birth rates. However, race/ethnicity was an important predictor of live births in the multivariate analysis, likely because the independent variable, SIR, was not itself adjusted for the varying of general population birth rates by race/ethnicity (i.e., blacks in general have higher birth rates, and Asians lower than whites, even in the general population).

An additional important predictor of live births was marital status. The proportion of women (42%) in our sample who were either married or living common-law is somewhat lower than the different national rates of countries included in our study (48–58%) (5–7). This, and/or other issues related to personal relationships, may be factors contributing to our observed lower birth rate in women with SLE compared with the general population.

Table 2. Live births in women with onset of systemic lupus erythematosus before age 50 years (n = 339)*

	Observed, no.	Expected, no.	SIR	95% CI
All births†	313	479	0.65	0.58–0.73
First births‡	156	170	0.92	0.78–1.07

* SIR = standardized incidence ratio; 95% CI = 95% confidence interval.
† Expected live births calculated from age-, country-, and calendar-specific general population rates.
‡ Expected live births calculated from age-, country-, calendar-, and parity-specific general population rates.

In addition, early menopause could theoretically contribute to low birth rates; the phenomenon of early menopause in SLE has been described by Cooper et al (8). The mean age at menopause (45.5 years; 95% CI 30.0–61.0) in our sample was perhaps slightly lower than the general population average (51 years) (9), although we did not have the precision to demonstrate statistical significance. Of course, peak birth rate generally occurs well before menopause, although there is a steady increase, in the developed world, for birth rates in women above the age of 35 years (10).

A limitation of our study is that we only had information on the date of first birth, not dates of subsequent births. Therefore, we were unable to estimate a SIR for all live births specifically before and after the SLE diagnosis. However, the SIR estimate, which focused on first births (89% of those occurred before SLE), showed no significant difference between observed and expected live births, suggesting that live births are not reduced before SLE diagnosis.

Moreover, as we only had information on the date of first birth, we were unable to establish the timing of disease activity, aPL status, and medication exposure respective to subsequent births. Therefore, we could not evaluate these covariates as time-varying, and this may explain why they were not strong predictors of live births.

Furthermore, although aPL have been associated with recurrent pregnancy losses, it is still unclear if they are associated with infertility in humans (11). A meta-analysis assessing the relationship of aPL with pregnancy rates and live birth rates following in vitro fertilization failed to show any negative association (11).

We used information on parity from the SLICC inception cohort questionnaire; this does not actually differentiate between stillbirths and live births, so we may have misclassified stillbirths as live births. This may have overestimated our live birth rate in women with SLE; hence, our results demonstrating lower live birth rates in women with SLE are likely conservative.

Several disease-related factors may contribute to reduced live birth rates in women with SLE. Although our study was not powered to assess these factors, since most of the births occurred prior to the SLE diagnosis, they warrant discussion. Women with no or mild disease activity in the 6 months preceding pregnancy are less likely to experience disease exacerbation (12). For this reason, it is generally recommended that women have stable disease

Table 3. Multivariate analyses exploring predictors of live births in women with systemic lupus erythematosus*

	Multivariate model	
	With all births, SIR (95% CI)	**With first births, SIR (95% CI)**
Race/ethnicity		
White (n = 207)	Reference	Reference
Black (n = 65)	1.47 (1.08–2.00)	1.67 (1.08–2.57)
Asian (n = 33)	0.50 (0.28–0.89)	0.62 (0.29–1.31)
Other (n = 34)	1.13 (0.67–1.90)	1.43 (0.79–2.59)
Marital status		
Single (n = 197)	Reference	Reference
Married/common-law (n = 142)	2.04 (1.52–2.74)	2.02 (1.40–2.93)
Age at diagnosis, years		
<30 (n = 135)	Reference	Reference
≥30 (n = 204)	0.78 (0.56–1.08)	1.06 (0.70–1.64)
Disease duration, years		
<5 (n = 289)	Reference	Reference
≥5 (n = 50)	0.87 (0.63–1.21)	1.00 (0.64–1.57)
Cyclophosphamide exposure		
Never (n = 300)	Reference	Reference
Ever (n = 39)	0.88 (0.56–1.38)	1.04 (0.61–1.77)
Antiphospholipid antibodies		
No (n = 156)	Reference	Reference
Yes (n = 105)	0.94 (0.67–1.33)	1.06 (0.71–1.59)
Disease activity (mean SLEDAI-2K score)		
<1 (n = 71)	Reference	Reference
1 to <5 (n = 180)	0.92 (0.66–1.28)	0.95 (0.63–1.43)
≥5 (n = 88)	0.82 (0.54–1.25)	0.93 (0.55–1.56)
Disease damage (SLICC score)		
0 (n = 216)	Reference	Reference
1 (n = 43)	1.46 (1.05–2.01)	1.37 (0.88–2.15)
≥2 (n = 41)	0.99 (0.65–1.51)	1.00 (0.59–1.69)

* Standardized incidence ratio (SIR) is calculated using live births calculated from age-, country-, and calendar-specific general population rates, and is adjusted for country. 95% CI = 95% confidence interval; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 update; SLICC = Systemic Lupus International Collaborating Clinics.

for 6 months before conceiving. In addition, certain drugs used to treat manifestations of SLE, such as methotrexate and mycophenolate mofetil, are contraindicated during pregnancy because of potential fetal harm (1). These medications must be discontinued or switched to safer ones in prevision of conception. Dependence on a medication to maintain disease control or uncontrolled active disease may delay motherhood and/or increase the interval between pregnancies in some women.

Moreover, in women with SLE, fertility might be impaired due to associated autoimmune anomalies, therapies (e.g., cyclophosphamide), and hormonal dysfunction (e.g., transient amenorrhea) (1). Nevertheless, there is a general notion that SLE does not diminish fertility in affected women, although this aspect of reproduction has never been properly measured. Most authors cite a 1974 study by Fraga et al (13), which reported a fertility rate in women with SLE that was comparable with an age-matched control group of healthy women. However, the fertility rate was calculated using the number of pregnancies in women who had at least 1 pregnancy. This largely overestimated the number of pregnancies per woman with SLE, since those who did not achieve any pregnancy were excluded.

Once pregnant, women with SLE are at increased risk of miscarriages and stillbirths. Approximately 20% of pregnancies in women with SLE will end in a miscarriage, compared with 9% in the general population (2). We observed the same proportion of miscarriage in our SLE sample. Some studies have demonstrated that this risk was present even before the SLE diagnosis, with almost a 2-fold increase compared with controls (1,2). The risk of stillbirths has also been shown to be elevated in several studies, with an approximately 3-fold increase compared with the general population (1). Obviously, miscarriages and stillbirths may directly contribute to a reduction in live births.

Women with SLE may also have impaired sexual function (14). Physical problems (e.g., chronic pain) and emotional problems (e.g., depression) can decrease sexual interest and reduce intercourse frequency. Disturbances of hormonal status by corticosteroid treatment and disease activity can reduce libido and interfere with successful reproduction (14). Partnership difficulties arising from disease-related stress can also contribute to a less active sexual life (13). In a study addressing this problem (15), 20% of SLE patients thought that their illness had driven their

family apart or worsened their relationship with their partner.

Faced with the potential risks of disease flare and/or adverse maternal and fetal outcomes, and considering the additional physical, social, and emotional demands related to the management of SLE, some women might choose not to have children. In a study assessing social functioning in 114 women with SLE, 27% viewed SLE as a barrier to childbearing (16). Common concerns included worries that pregnancy might exacerbate the disease, that medications or the disease might harm the fetus, and that the disease might interfere with childcare.

In conclusion, compared with the general population, we found substantially decreased live birth rates in women with SLE, whose diagnosis occurred during their reproductive years. Further study of the relative importance of demographic, social, and clinical factors will help confirm which subgroups of women with SLE may be at greatest risk for decreased birth rates.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Vinet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Vinet, Clarke, Gordon, Urowitz, Pineau, Wallace, Bruce, van Vollenhoven, Bernatsky.

Acquisition of data. Vinet, Clarke, Gordon, Urowitz, Hanly, Isenberg, Rahman, Wallace, Alarcón, Petri, Dooley, Kalunian, Maddison, Aranow, Bernatsky.

Analysis and interpretation of data. Vinet, Clarke, Gordon, Hanly, Wallace, Aranow, Bernatsky.

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CONCISE REPORT

A population-based assessment of live births in women with systemic lupus erythematosus

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ABSTRACT

Objectives The authors aim to calculate the number of live births, before and after systemic lupus erythematosus (SLE) diagnosis, in women diagnosed during their reproductive years and to compare this with general population rates.

Methods The authors identified women with SLE using Quebec administrative databases (1 January 1994 to 31 December 2003). The authors determined the number of live births, and calculated the standardised incidence ratio (SIR) of observed to expected live births.

Results 1334 women with SLE were identified. Overall, the number of live births over the interval (559) was below that which would be expected (708) (SIR 0.79; 95% CI 0.73 to 0.86). Compared with the general population, live births were substantially lower after SLE diagnosis (SIR 0.62; 95% CI 0.55 to 0.70) than before diagnosis (SIR 1.01; 95% CI 0.90 to 1.13).

Conclusion After diagnosis, women with SLE have substantially fewer live births than the general population.

INTRODUCTION

Upon being diagnosed as having systemic lupus erythematosus (SLE), women of reproductive age often want to know if their disease will limit their ability to have children. Up to now, research has focused on a limited but important aspect of this question—estimating the proportion of SLE pregnancies ending in live births. One further step in providing an adequate answer would be to assess live birth rates in women with SLE.

The live birth rate (also known as the fertility rate) is a useful demographic statistic and is defined as the number of live births per 1000 women of reproductive age (usually between 15 and 45 years old) in a given year.[1] The live birth rate is thus influenced by two key reproductive outcomes: the number of pregnancies and the number of live births in a group of women. Multiple disease-related factors may limit live birth rates in women with SLE (see online supplementary text).[2]

The standardised incidence ratio (SIR), which is the ratio of the observed number of events in a sample divided by the expected number of events, allows us to directly compare the live birth rate in women with SLE to the live birth rate in the general population.[3] As the live birth rate in the general population is usually recorded according to age group and calendar time, the SIR offers direct comparison of women with SLE, at different reproductive stages and born at different periods, to the general population by providing a summarised measure. Estimating such a measure should definitively answer whether having SLE influences the number of children affected women have.

Previously, we have performed a study determining the SIR of live births in women from an inception cohort of SLE,[4] using general population rates as a reference. We observed that women diagnosed as having SLE during their reproductive period had substantially decreased live birth rates compared to the general population (SIR 0.65; 95% CI 0.58 to 0.73). However, this study was limited in that we had information only on date of first birth, not on dates of subsequent births. Thus, we were unable to estimate a SIR for live births specifically before and after SLE diagnosis.

To further investigate if live birth rates are reduced after SLE diagnosis, we performed a population-based study using administrative databases. Our primary objectives were to calculate the number of live births, before and after SLE diagnosis, in a cohort of women diagnosed as having SLE during their reproductive years and to compare this with general population rates using SIR.

SUBJECTS AND METHODS

We identified women with SLE using Quebec administrative databases (Med-Echo and Régie de l'assurance maladie du Québec (RAMQ) physician billing databases, 1 January 1994 to 31 December 2003), which cover all healthcare beneficiaries. Incident SLE cases were women with ≥1 hospitalisation with either a primary or a secondary diagnosis of SLE or ≥2 physicians' claims for SLE within any 2-month-to-2-year period, with no prior diagnosis of SLE in the 5 years preceding the interval. To assess women diagnosed as having SLE during their reproductive period, we only included women aged 15–35 years on 1 January 1994.

We determined the number of live births during the interval as defined by diagnostic and procedure codes for delivery in the Med-Echo and RAMQ physician databases, respectively. As mentioned previously, the SIR is the ratio of the observed number of live births in a sample divided by the expected number of live births. We determined the expected number of live births as follows: we summed the years of follow-up from the subjects' age at the start of the study interval up to the age

Table 1 Patients' characteristics (n=1334)

Characteristics	Women
Age at diagnosis, years (mean±SD)	28.9±8.0
Age at first birth, years (mean±SD)	28.6±5.1
Disease duration ≥5 years, n (%)	711 (53.3)
Living in a rural region, n (%)	288 (21.6)
Antiphospholipid syndrome, n (%)	321 (24.1)
Prior hospitalisation for SLE, n (%)	479 (35.9)
Renal disease, n (%)	148 (11.1)

Characteristics were determined at the end of the follow-up.
SLE, systemic lupus erythematosus.

of 45 years (or the oldest age attained at the end of the study period). For subjects who died during the interval, years of follow-up were summed up to the time of death. We applied age-specific general population birth rates, for the relevant calendar periods, to these years of follow-up to obtain the expected number of births. We then calculated the SIR of observed to expected live births for the overall study interval, as well as before and after SLE diagnosis.

We performed a multivariate Poisson regression to explore potential predictors of live births in women with SLE. Time-dependent predictors, assessed at the time of delivery, included prior hospitalisation with a primary diagnosis of SLE, renal disease (ie, RAMQ billing code for renal biopsy), antiphospholipid syndrome (ie, *ICD-9 (International Classification of Diseases, 9th Revision)* code for antiphospholipid antibodies and/or any thromboembolic events in either databases), disease duration ≥5 years and residence in rural regions (ie, census <10 000 inhabitants). Because renal disease was defined using renal biopsy, which almost always requires hospitalisation, we included an interaction term between renal biopsy and hospitalisation for SLE in the multivariate model.

We corrected our model for clustering of reproductive outcomes and performed a sensitivity analysis using first births (see online supplementary text).[5]

The McGill University Research ethics board approved this study.

RESULTS

One thousand three hundred and thirty-four women with SLE were identified (table 1). Overall, the number of live births over the interval (559) was below that which would be expected (708) (SIR 0.79; 95% CI 0.73 to 0.86) (table 2). Compared with the general population, live births were substantially lower after SLE diagnosis (SIR 0.62; 95% CI 0.55 to 0.70) than before diagnosis (SIR 1.01; 95% CI 0.90 to 1.13).

In multivariate analyses of potential predictors of live births in women after SLE diagnosis (table 3), prior hospitalisation for SLE (RR 0.49; 95% CI 0.35 to 0.68) was associated with markedly decreased live births. There were trends for fewer live births in women with disease duration ≥5 years (RR 0.89; 95% CI 0.67 to 1.18) and in those living in rural regions (RR 0.83; 95% CI 0.61 to 1.13).

We did not definitively observe a decrease in live births independently attributable to age at SLE diagnosis ≥30 years (RR 1.10; 95% CI 0.81 to 1.47), antiphospholipid syndrome (RR 0.91; 95% CI 0.65 to 1.29) or renal disease (RR 0.84; 95% CI 0.34 to 2.04). In addition, we did not establish any interaction between renal disease and prior hospitalisation for SLE (RR 1.95; 95% CI 0.72 to 5.31). The multivariate analysis restricted to first births gave similar results, confirming the precision of our model for all births.

Table 2 Live births (n=1334) in women with SLE diagnosis before 45 years of age

	Observed	Expected*	SIR	95% CI
Overall	559	708	0.79	0.73 to 0.86
Before SLE diagnosis	309	305	1.01	0.90 to 1.13
After SLE diagnosis	250	403	0.62	0.55 to 0.70

*Expected live births were calculated from age- and calendar-specific general population rates.
SIR, standardised incidence ratio; SLE, systemic lupus erythematosus.

DISCUSSION

We observed that women diagnosed as having SLE during their reproductive period have substantially decreased live birth rates after diagnosis compared to the general population. We did not observe decreased live births in women with SLE prior to diagnosis. The most important predictor of decreased live births after SLE diagnosis was prior hospitalisation for SLE, which likely indicates more severe/active disease.

We were unable to establish an independent association with renal disease, traditionally recognised as a marker of disease activity/severity,[6] on live birth rates. The definition we used for renal disease relied on renal biopsy, which often requires hospitalisation. Since the primary discharge diagnosis in patients hospitalised to undergo a renal biopsy may have been SLE, the renal disease effect estimate may have been intermingled with the effect estimate for prior SLE hospitalisation. To account for this possibility, we included in our model an interaction term for renal disease and prior hospitalisation, but it failed to demonstrate an effect of renal disease, with or without prior hospitalisation, on live birth rates. Although our definition of renal disease aimed for high specificity, likely capturing patients with severe nephritis, it may have lacked sensitivity, potentially missing milder forms of nephritis. Only 11% of our SLE cohort was identified as having renal disease; this limited our power to find a small effect.

We were unable to demonstrate a decrease in live births due to antiphospholipid syndrome. No *ICD-9* code exists for this syndrome, and no claim-based definition has been validated. Thus, our definition, based on antiphospholipid antibodies and/or thromboembolic events, may have lacked specificity, biasing our effect estimate towards the null value due to non-differential misclassification.

We observed potentially decreased live births in women living in rural regions. This may be explained by limited healthcare accessibility, resulting in adverse pregnancy outcomes, deliberate decision to avoid pregnancy and/or inappropriate counselling on pregnancy. Moreover, this difference may reflect variations in racial distribution between urban and rural regions in Quebec, the latter being predominantly populated by Caucasians.[7] Since Caucasians are known to have one of the lowest live birth rates[8] and since our multivariate analysis did not account for race, as this variable was not present in the database, this may explain reduced RR for live births in women from rural regions. However, it is unlikely that failure to adjust for race would explain our primary results, the SIR for live births before and after diagnosis. Indeed, in our previous study,[4] decreased live birth rates in women with SLE (compared to the general population) persisted after applying race-specific birth rates. Furthermore, non-Caucasian groups such as African–Americans and Hispanics, who have increased live birth rates compared to Caucasians,[8] are generally over-represented in North American SLE cohorts (due to their higher rate of SLE).[9 10] Thus, if anything, our results are likely conservative (see online supplementary text for further discussion of limitations).

Table 3 Multivariate analyses exploring predictors of live births in women with SLE (n=1334)

	Multivariate model with all births, RR (95% CI)	Multivariate model with first births, RR (95% CI)
Age at diagnosis		
Less than 30 years	Reference 1.10 (0.81 to 1.47)	Reference 1.13 (0.69 to 1.86)
30 years or more		
Disease duration		
Less than 5 years	Reference 0.89 (0.67 to 1.18)	Reference 0.91 (0.59 to 1.41)
5 years or more		
Living in a rural region		
No	Reference 0.83 (0.61 to 1.13)	Reference 0.68 (0.42 to 1.09)
Yes		
Antiphospholipid syndrome		
No	Reference 0.91 (0.65 to 1.29)	Reference 0.64 (0.36 to 1.12)
Yes		
Prior hospitalisation for SLE		
No	Reference 0.49 (0.35 to 0.68)	Reference 0.57 (0.33 to 0.96)
Yes		
Renal disease		
No	Reference 0.84 (0.34 to 2.04)	Reference 0.97 (0.24 to 3.98)
Yes		
Renal disease + prior hospitalisation for SLE		
No	Reference 1.95 (0.72 to 5.31)	Reference 1.93 (0.40 to 9.26)
Yes		

SLE, systemic lupus erythematosus.

In conclusion, our findings indicate that live birth rates are substantially reduced (compared to the general population) after diagnosis in women with SLE and that disease-related factors, such as prior hospitalisation for SLE, potentially play an important role. These results prompt future research to further characterise disease-related, demographic and psychosocial factors contributing to decreased live birth rates in women with SLE.

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Competing interests None.

Ethics approval Ethics approval was obtained from the McGill University ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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A population-based assessment of live births in women with systemic lupus erythematosus

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Increased Congenital Heart Defects in Children Born to Women With Systemic Lupus Erythematosus

Results From the Offspring of Systemic Lupus Erythematosus Mothers Registry Study

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Background—In a large population-based study, we aimed to determine whether children born to women with systemic lupus erythematosus (SLE) have an increased risk of congenital heart defects (CHDs) in comparison with children born to women without SLE.

Methods and Results—The Offspring of SLE Mothers Registry (OSLER) includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's healthcare databases (1989–2009), and a randomly selected control group of women, matched ≥4:1 for age and year of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained CHD based on ≥1 hospitalization or physician visit with relevant diagnostic codes, within the first 12 months of life. We performed multivariable logistic regression analyses, using the generalized estimating equation method, to adjust for relevant covariates. Five hundred nine women with SLE had 719 children, whereas 5824 matched controls had 8493 children. In comparison with controls, children born to women with SLE experienced more CHD (5.2% [95% confidence interval (CI), 3.7–7.1] versus 1.9% [95% CI, 1.6–2.2], difference 3.3% [95% CI, 1.9–5.2]). In multivariable analyses, children born to women with SLE had a substantially increased risk of CHD (odds ratio, 2.62; 95% CI, 1.77–3.88) in comparison with controls. In addition, in comparison with controls, offspring of SLE mothers had a substantially increased risk of having a CHD repair procedure (odds ratio, 5.82; 95% CI, 1.77–19.09).

Conclusions—In comparison with children from the general population, children born to women with SLE have an increased risk of CHD, and an increased risk of having a CHD repair procedure, as well. **(*Circulation*. 2015;131:149-156. DOI: 10.1161/CIRCULATIONAHA.114.010027.)**

Key Words: epidemiology ■ heart defects, congenital ■ lupus erythematosus, systemic ■ pregnancy

Systemic lupus erythematosus (SLE) predominantly occurs in women of childbearing age, with prevalence estimates of ≈1.5/1000 in females aged 18 to 44 years.[1] This disease can cause considerable morbidity during pregnancy. Pregnant women with SLE and those contemplating pregnancy often ask if their disease will affect their baby. Although several studies have evaluated obstetric outcomes in lupus pregnancy, little is known about the risk of congenital anomalies.

Clinical Perspective on p 156

Congenital heart defects (CHDs) are the most frequent type of birth defects, accounting for approximately one-third of all congenital anomalies[2]; they are associated with substantial child morbidity.[3] In utero exposures, such as maternal illnesses and medications, are thought to play an important role in the yet to be fully elucidated etiology of CHD.[4] In particular, a recent study suggests a 3-fold increased risk of CHD in children born to mothers with various systemic connective tissue disorders, including SLE.[5] However, the investigators did not specifically assess the SLE effect estimate for the risk of CHD and did not control for medication exposures. Certain drugs used to treat SLE manifestations, such as methotrexate and mycophenolate mofetil, are known teratogens, and affected women might be inadvertently exposed to these agents during pregnancy, potentially increasing the risk of CHD.[6]

Only very few uncontrolled observational studies have assessed CHD in offspring of mothers with SLE. Notably, in a study of fetal echocardiography in a small number of SLE pregnancies,[7] 7.5% of fetuses had a CHD, which is >5-fold what is usually observed among live births from the general population (0.6%–1.3%), although that is clearly not an equivalent comparison group.[8] Investigators have also observed CHD in 16% to 42% of children with congenital heart block born to mothers with anti-Ro/SSA antibodies, after excluding cases with CHD

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that could have caused congenital heart block.[9–13] Although the prevalence of CHD was lower in children born to mothers with anti-Ro/SSA antibodies who did not develop congenital heart block (2.8%), the frequency was still substantially higher than in the general population.[9] In such studies, the most frequently observed CHDs were atrial septal defects (ASDs), ventricular septal defects (VSDs), and valve anomalies.[9–13]

Given the paucity of existing literature, we aimed, in a large population-based study, to determine whether children born to women with SLE have an increased risk of CHD in comparison with children born to women without SLE. In addition, we aimed to determine if the offspring of SLE mothers have an increased risk of particular CHD subtypes, including ASD, VSD, and valve anomalies, in comparison with the offspring born to unaffected mothers.

Methods

Study Design and Subjects

The Offspring of SLE Mothers Registry (OSLER) is a population-based cohort of 719 children born to mothers with SLE, matched to 8493 control children. To create this large cohort, we identified all women with SLE who had ≥1 hospitalization for a delivery resulting in a stillbirth or live birth, between January 1989 and December 2009, using data from the Quebec Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) hospitalization and Régie de l'Assurance Maladie du Québec (RAMQ) physician billing databases.

MED-ECHO is the administrative database collecting information on all hospitalizations in Quebec since 1987 and provides, for each hospitalization, a primary discharge diagnosis and ≤15 nonprimary diagnoses, captured as *International Classification of Diseases, Ninth Revision* (ICD-9) codes, and since 2006, *International Classification of Diseases, Tenth Revision* (ICD-10) codes. The RAMQ billing database records 1 physician-assigned diagnosis, based on ICD-9 codes, for each physician encounter.

Exposure of Interest

Women were identified as SLE cases, based on a validated definition,[14] with the use of 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 nonprimary, before the delivery; (2) a diagnosis of SLE, either primary or nonprimary, 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, before the delivery. From these databases, a general population control group was composed of women individually matched ≥4:1 for age and year of delivery, who did not have a diagnosis of SLE before or at the time of delivery.

Mother–child linkage was done by using the encrypted mother's number, which is present in every child's file in the RAMQ and MED-ECHO databases, and where it remains through childhood, leading to very few linkage failures (<2%). Those children born live were the basis of the OSLER cohort for outcome ascertainment, one being the exposed group consisting of children born to women with SLE, and the other being the control group consisting of children born to women without SLE. Stillbirths were not included because a substantial proportion of stillbirths in Quebec result from pregnancy termination, for which no information for our outcome of interest is recorded either for SLE mothers or for controls (see online-only Data Supplement).[15]

Outcome Assessment

The cohort of children described above was linked to the MED-ECHO and RAMQ databases to determine hospitalizations and all diagnoses occurring throughout the study interval of these offspring. This study interval spanned from birth to the first of the following: end of eligibility for RAMQ coverage (ie, migration from Quebec), event of interest (eg, CHD), age 1, death, or end of study (ie, December 31, 2009).

Our ascertainment of CHD in live-born babies was based on the presence, at birth or within the first 12 months of life, of ≥1 ICD-9 codes 745, 746, and 7471 to 7474 and ICD-10 codes Q20 to Q26, using the methodology developed by the European Surveillance of Congenital Anomalies network.[16] The use of ICD-9 and ICD-10 codes for identification of CHD has been previously validated in Quebec's administrative databases.[17] We further excluded subjects with ICD-9 and ICD-10 codes referring to congenital heart block and patent ductus arteriosus as the only CHD. However, subjects with a diagnosis of congenital heart block and patent ductus arteriosus and any other CHD were included as cases. ASD, VSD, and valve anomalies were defined based on ≥1 relevant diagnostic code (see online-only Data Supplement). We included records of CHD diagnosed within the first 12 months of life to capture events with delayed detection or registration.

Assessing Relevant Covariates

For all mothers in our study, we reviewed the MED-ECHO and RAMQ data to identify specific preexisting and current comorbidities (ie, hypertension, pregestational diabetes mellitus, asthma) recorded in the 2 years before the time of delivery, and obstetric complications, as well, such as gestational diabetes mellitus, at the time of the hospitalization for delivery. The diagnosis of specific comorbidities listed above was based on ICD-9 and ICD-10 codes indicating ≥1 hospitalization or ≥2 physician visits, at least 8 weeks apart, for the diagnosis of interest, as per previously validated methodology.[18,19]

Available through the Institut de la Statistique du Québec were data on the demographics of the parents at the time of delivery, including maternal education, and maternal and paternal birthplace, maternal language, and language spoken at home, as well, which were used to establish the race/ethnicity of the offspring (see online-only Data Supplement). These demographic data were used in our analyses as covariates.

Comprehensive and valid data on drug exposures are available from the RAMQ prescription (RAMQ-Rx) database, but only for beneficiaries of the public drug plan.[20] The RAMQ-Rx plan covers recipients of social assistance and workers and their families who do not have access to private drug insurance. In our cohort, 22% of exposed children and 21% of controls were born to a mother with RAMQ-Rx plan coverage throughout pregnancy.

In this subgroup, we obtained all information on the prescription of certain types of medications, including corticosteroids, antimalarials, immunosuppressives, antidepressants, and anticonvulsants. It is noteworthy that there is no information recorded on intravenous cyclophosphamide exposure in the RAMQ-Rx database, because this medication is administered in hospital. We used gestational age recorded at birth to calculate back to the estimated start of the gestational period, then determined whether a medication exposure of interest ever occurred during pregnancy based on ≥1 prescription filled at any time during gestation.

Statistical Analysis

We calculated the prevalence and computed the odds ratios (ORs) for all types and specific subtypes of CHD in the group of children born to mothers with SLE versus the control group, performing both univariable and multivariable regression analyses estimated with generalized estimating equations.[21] Missing data on education and race/ethnicity covariates, occurring in <6% of subjects, were handled by using multiple imputation (see online-only Data Supplement).

In these analyses, we matched SLE exposed and unexposed children for maternal age group and calendar year of delivery, but we also further adjusted for maternal age and calendar year to control for potential confounding by these variables (see online-only Data Supplement). In addition, we adjusted for relevant demographic factors and maternal comorbidities, including the following: sex of child, birth order, maternal education, race/ethnicity, pregestational and gestational diabetes mellitus, maternal hypertension, and asthma. In the subsample with RAMQ-Rx plan coverage, we also adjusted for in utero maternal medication exposures, including corticosteroids (ie, oral or intravenous corticosteroids), antimalarials (ie, hydroxychloroquine or chloroquine), immunosuppressives (ie, azathioprine, mycophenolate mofetil, mycophenolate sodium, and methotrexate), and any types of antidepressants. Of note, we excluded exposure to

anticonvulsants from the subsample multivariable model because no CHD case was recorded for this covariate.

Moreover, we performed a sensitivity analysis to account for the possibility of detection bias. Indeed, the offspring of SLE mothers are more likely to undergo fetal echocardiography as part of routine screening to detect congenital heart block in those exposed in utero to maternal anti-SSA/Ro and anti-SSB/La antibodies, which are present in up to 40% of women with SLE.[22] Hence, CHD might be more easily detected in children born to women with SLE than in controls, leading to an overestimation of the association. Thus, to account for this possibility, we reran the analysis excluding children who had ≥1 fetal echocardiography.

In addition, to investigate the clinical impact of a potentially increased risk of CHD in SLE offspring versus controls, we further assessed the risk of CHD repair procedures (see online-only Data Supplement), adjusting for the potential confounders mentioned above, with the exception of medication, owing to the small number of procedure events in the subsample with public drug coverage.

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. The first author takes full responsibility for the accuracy and completeness of the data.

Results

Five hundred nine women with SLE had 719 children, whereas 5824 matched controls had 8493 children. Mean maternal age in the overall sample of mothers and mean SLE disease duration were, respectively, 30.3 (standard deviation[SD], 5.0) and 3.7 (SD, 4.0) years (Table 1). Mothers with SLE had similar demographic characteristics in comparison with control mothers, with the exception of race/ethnicity because they were less likely to be white (as expected, because black and Asian race/ethnicity may predispose to SLE).[1] In addition, mothers with SLE had more comorbidities and experienced substantially more obstetric complications, such as preterm births and preeclampsia/eclampsia, in comparison with control mothers. In utero drug exposures were more frequent in SLE offspring than in controls, with exposures to corticosteroids and antimalarials being the most common drugs prescribed during SLE pregnancies. Among the 11 children with in utero immunosuppressive exposures, all were exposed to azathioprine, with 7/11 having ≥3 records of the drug dispensed, and 1 child was additionally exposed to mycophenolate mofetil, albeit with only 1 record of the drug dispensed early in gestation.

In comparison with controls, children born to women with SLE experienced more CHD (5.1% [95% confidence interval (CI), 3.7–7.1] versus 1.9% [95% CI, 1.6–2.2], difference 3.2% [95% CI, 1.9–5.2]), including more ASD, VSD, and valve anomalies (Table 2). In offspring with maternal drug coverage throughout pregnancy (n=1925), we observed 5 cases of CHD (4 born to SLE mothers and 1 to a control mother) among the 46 children exposed to corticosteroids, and 1 case of CHD in the 11 children exposed to immunosuppressives, all born to SLE mothers.

In multivariable analyses including all children (n=9212), children born to women with SLE had a substantially increased risk of CHD (OR, 2.62; 95% CI, 1.77–3.88) in comparison with controls (Table 3). Specifically, offspring of SLE mothers had substantially increased odds of ASD (OR, 3.32; 95% CI, 1.97–5.77), VSD (OR, 2.50; 95% CI, 1.31–4.75), and valve anomalies (OR, 2.95; 95% CI, 1.23–7.07) in comparison with controls. Other predictors of CHD included pregestational diabetes mellitus and asthma (Table 3).

There was an imbalance between the 2 groups in terms of fetal echocardiography, with 16.3% of SLE offspring having ≥1 fetal echocardiography in comparison with 2.5% of control children. When accounting for the possibility of detection bias by excluding children with ≥1 fetal echocardiography (n=331) from the multivariable analyses, adjusted effect estimates were similar to the primary multivariable analysis results for CHD and all subtypes of CHD (Table 4).

Table 1. Characteristics of the SLE Offspring and Control Children (n=9212) in Quebec's Administrative Databases, Canada, 1989 to 2009

Characteristics	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
Maternal characteristics			
Mean age, y (SD)	30.2 (5.1)	30.3 (5.0)	0.56
Mean education, y (SD)	14.0 (3.1)	13.8 (3.1)	0.07
Marital status, n (%)			
Couple	576 (80.1)	6904 (81.3)	0.65
Single	50 (7.0)	523 (6.2)	
Unknown	93 (12.9)	1066 (12.6)	
Comorbidities, n (%)			
Hypertension	47 (6.5)	87 (1.0)	<0.0001
Asthma	38 (5.3)	240 (2.8)	0.0002
Diabetes mellitus	23 (3.2)	143 (1.7)	0.003
Depression	11 (1.5)	38 (0.4)	0.0001
Paternal characteristics			
Mean age, y (SD)	33.2 (5.8)	33.3 (5.9)	0.47
Demographic characteristics			
Male sex, n (%)	402 (55.9)	4377 (51.5)	0.02
Ethnicity, n (%)			
White	444 (61.8)	6226 (73.3)	<0.0001
Other	275 (38.2)	2268 (26.7)	
Obstetric characteristics			
Mean gestational age, wk (SD)	37.7 (2.9)	38.8 (1.9)	<0.0001
Mean birth weight, g (SD)	2976 (707)	3367 (566)	<0.0001
Birth order, n (%)			
1	308 (42.8)	2333 (27.5)	<0.0001
≥2	411 (57.2)	6160 (72.5)	
Obstetric complications, n (%)			
Preterm birth	157 (22,0)	614 (7.3)	<0.0001
Small for gestational age	120 (16.7)	694 (8.2)	<0.0001
Gestational diabetes mellitus	30 (4.2)	263 (3.1)	0.11
In utero medication information			
Public drug coverage, n (%)	155 (21.6)	1770 (20.8)	0.65
Corticosteroids	34 (21.9)*	12 (0.7)†	<0.0001
Antimalarials	25 (16.1)*	1 (0.1)†	<0.0001
Immunosuppressives	11 (7.1)*	0 (0.0)†	<0.0001
Antidepressants	11 (7.1)*	52 (2.9)†	0.005
Anticonvulsants	1 (0.6)*	7 (0.4)†	0.49

SD indicates standard deviation; and SLE, systemic lupus erythematosus.

*Denominator used for proportion is number of children born to SLE mothers with public drug coverage during pregnancy.

†Denominator used for proportion is number of children born to control mothers with public drug coverage during pregnancy.

Table 2. Frequency of Congenital Heart Defects and Subtypes in SLE Offspring and Control Children (n=9212) in Quebec's Administrative Databases, Canada, 1989 to 2000

Types	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
Any CHDs	37 (5.1)	159 (1.9)	<0.0001
Cardiac septal defects, n (%)	29 (4.0)	109 (1.3)	<0.0001
ASDs	21 (2.9)	68 (0.8)	<0.0001
Isolated* ASD	11 (1.5)	39 (0.5)	0.001
VSDs	12 (1.7)	56 (0.7)	0.002
Isolated VSD	6 (0.8)	38 (0.5)	0.15
Cardiac valve anomalies	7 (1.0)	26 (0.3)	0.009
Isolated valve anomalies	3 (0.4)	13 (0.2)	0.12
Other CHDs			
Other CHDs without ASD, VSD, and valve anomalies†	14 (1.9) 4 (0.6)	54 (0.6) 33 (0.4)	0.0006 0.53
CHDs with ≥1 extracardiac major congenital anomalies	5 (0.7)	15 (0.2)	0.02

Values are presented as n (%). ASD indicates atrial septal defect; CHD, congenital heart defect; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

*Isolated is defined as a specific subtype of CHD occurring without any other subtype of CHD.

†Among cases with other CHDs, but without ASD, VSD, and valve anomalies, the most frequent diagnosis in SLE offspring cases was pulmonary artery anomaly (2/4), whereas, in control cases, it was CHD not otherwise specified (12/34).

In the subsample analysis controlling for maternal medications (Table 5), although the effect estimates for the association of ASD (OR, 2.05; 95% CI, 0.66–6.37) with maternal SLE remained similar to the primary multivariable analysis result, the 95% CI was wide and included the null value owing to reduced sample size (155 SLE offspring and 1770 controls). In addition, after adjusting for maternal medication exposures, results were inconclusive for the risk of CHD and specifically VSD in SLE offspring in comparison with controls. However, we observed an effect of corticosteroid exposure on the likelihood of CHD (OR, 5.65; 95% CI, 1.65–19.34), after adjusting for both pregestational and gestational diabetes mellitus. Of note, we could not perform a multivariable analysis adjusting for medication exposure for the outcome of valve anomaly, because no case was observed in SLE offspring in the subsample with provincial drug coverage.

Among children with CHD, those born to SLE mothers had more CHD repair procedures than controls (10.5% [95% CI, 2.9–24.8] versus 3.7% [95% CI, 1.4–7.9]; Table 6). In addition, in comparison with controls, offspring of SLE mothers had a substantially increased likelihood of having a repair procedure for any type of CHD (OR, 5.82; 95% CI, 1.77–19.09), and specifically having a cardiac septal defect repair procedure (OR, 4.95; 95% CI, 1.22–20.07), after adjusting for relevant covariates.

Discussion

In comparison with children from the general population, children born to women with SLE have an increased risk of CHD, including a specifically increased risk of ASD, VSD, and valve anomalies. In addition, offspring of SLE mothers have substantially increased odds of CHD repair procedures in comparison with children from the general population. The effect of SLE on all types of CHD does not seem to be explained by detection bias and might be independent of medication exposures. Because of the limited power afforded by the sample of subjects who had provincial drug coverage, the findings of analyses limited to this subgroup are inconclusive, although they still point to an increased risk of CHD, regardless of medication exposure.

We found an association between in utero exposure to corticosteroids and CHD, although the CI was wide. Several studies have investigated the potential association between in utero corticosteroid exposure and congenital anomalies, but despite a potential and still controversial increased likelihood of oral cleft defects, no excess risk has been seen for other types of congenital anomalies, in particular, cardiac.[23] The effect of corticosteroid exposure on CHD observed in our study might be explained in part by confounding by disease severity. Indeed, if SLE itself has a causal effect on CHD (eg, mediated through inflammation and autoantibodies), and women with more severe SLE are more likely to have active disease during pregnancy and require corticosteroids for disease control, then confounding by disease severity is likely to have occurred and account for some of the apparent effect of corticosteroid exposure.

We observed that pregestational diabetes mellitus was a potentially important predictor of CHD and all subtypes investigated. It is well recognized that, in the conception period and the first trimester of pregnancy, maternal hyperglycemia can cause diabetic embryopathy resulting in major congenital anomalies.[24] The most frequent type of major congenital anomalies seen in women with pregestational and gestational diabetes mellitus is CHD.[24] Previous studies have shown that the likelihood of CHD was highest in women with pregestational diabetes mellitus in comparison with those with gestational diabetes mellitus (respectively, 3-fold and 1.5-fold increased risk relative to healthy women).[25,26] We observed similar effect estimates, suggesting that our findings are consistent with published literature on diabetic embryopathy.

The strength of our study resides in the use of Quebec's administrative databases, which collect information on all deliveries performed in the province, allowing us to create OSLER, the largest cohort of children born to mothers with SLE ever assembled. In addition, Quebec's administrative databases are a valid data source for the conduct of observational studies, with previous work from our group showing that our SLE case definition has a very high specificity (0.99).[14] Of note, 16% of SLE children were exposed in utero to antimalarial drugs, which are used to prevent SLE flare. This is comparable to exposure in SLE pregnancies observed over a similar time period and from a well-established tertiary care lupus cohort, where 22% were exposed to antimalarials beyond the first trimester.[27] Furthermore, a recent study assessed the validity of pregnancy-related variables recorded in the RAMQ, MED-ECHO, and ISQ databases, such as gestational age and live births, and showed very high sensitivity (0.97–0.99) and specificity (0.92–0.98) for all the variables examined, concluding that these administrative databases are a valid data source for pregnancy-related variables.[28]

We used a widely accepted definition of CHD based on ICD-9 and ICD-10 diagnostic codes established by the European Surveillance of Congenital Anomalies network.[16] In addition, a recent study assessed the validity of ICD-9 and ICD-10 diagnostic codes for major congenital anomalies, including CHD, recorded in Quebec's administrative databases.[17] Those investigators used

Table 3. Multivariable Analyses of the Risk of All Types of Congenital Heart Defects and Subtypes in the Overall Sample of Children (n=9212) from Quebec's Administrative Databases, Canada, 1989 to 2009

Covariates	Any CHD OR (95% CI)	ASD OR (95% CI)	VSD OR (95% CI)	Valve Anomalies OR (95% CI)
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	2.62 (1.77–3.88)	3.32 (1.97–5.57)	2.50 (1.31–4.75)	2.95 (1.23–7.07)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.06 (0.79–1.42)	1.00 (0.66–1.53)	1.30 (0.80–2.11)	0.71 (0.35–1.44)
Education				
≤ High school	Reference	Reference	Reference	Reference
≥ College	0.94 (0.68–1.30)	0.87 (0.55–1.38)	1.16 (0.68–1.98)	1.01 (0.47–2.20)
Ethnicity				
White	Reference	Reference	Reference	Reference
Other	1.28 (0.90–1.81)	1.35 (0.84–2.19)	1.47 (0.85–2.55)	1.30 (0.57–2.94)
Pregestational diabetes mellitus				
No	Reference	Reference	Reference	Reference
Yes	2.05 (0.99–4.23)	2.54 (1.03–6.27)	3.56 (1.24–10.17)	2.14 (0.46–10.02)
Gestational diabetes mellitus				
No	Reference	Reference	Reference	Reference
Yes	1.17 (0.54–2.54)	1.01 (0.31–3.26)	3.05 (1.28–7.25)	2.07 (0.48–8.96)
Hypertension				
No	Reference	Reference	Reference	Reference
Yes	1.59 (0.70–3.64)	2.04 (0.76–5.53)	0.56 (0.07–4.24)	0.91 (0.11–7.66)
Asthma				
No	Reference	Reference	Reference	Reference
Yes	2.76 (1.63–4.71)	2.00 (0.89–4.53)	1.24 (0.38–4.02)	4.25 (1.57–11.53)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defects.

medical chart as the gold standard and evaluated the performance of relevant diagnostic codes recorded during the first year of life in children born to asthmatic women in comparison with children born to nonasthmatic women. Results were similar between both groups; in particular, both the positive predictive value of CHD and the negative predictive value for any type of congenital anomalies were high (both >94%).[17] Because asthma is one of the most frequent chronic diseases encountered during pregnancy, with potential for disease exacerbation, similar to SLE in pregnancy, it is of interest to note that there was no differential ascertainment of congenital anomalies in offspring of affected women in comparison with controls. We would hope, although we cannot be sure, that there would similarly be no differential ascertainment of congenital anomalies in the offspring of women affected by SLE in comparison with controls.

Still, we accounted for the possibility of detection bias owing to the more frequent use of fetal echocardiography in SLE pregnancies, which is a considerable strength of our study. After

Table 4. Adjusted Effect Estimates of the Risk of All Types of Congenital Heart Defects and Subtypes in the Overall Sample of Children (n=9212) and Subsample Excluding Children With at Least 1 Fetal Echocardiography (n=8881), From Quebec's Administrative Databases, Canada, 1989 to 2009

Sample	Any CHD OR* (95% CI)	ASD OR* (95% CI)	VSD OR* (95% CI)	Valve Anomalies OR* (95% CI)
All children (n=9212)				
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	2.62 (1.77–3.88)	3.32 (1.97–5.57)	2.50 (1.31–4.75)	2.95 (1.23–7.07)
Excluding children with ≥1 fetal echocardiography (n=8881)				
Maternal SLE				
No	Reference	Reference	Reference	Reference
Yes	1.95 (1.18–3.23)	2.41 (1.23–4.75)	2.06 (0.96–4.43)	2.32 (0.67–8.05)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

*Adjusted for maternal age, calendar year, sex, education, ethnicity, pregestational diabetes mellitus, gestational diabetes mellitus, hypertension, and asthma.

Table 5. Multivariable Analyses of the Risk of All Types of Congenital Heart Defects and Subtypes in Subsample of Children With Public Drug Coverage (n=1925) in Quebec's Administrative Databases, Canada, 1989 to 2009

Covariates	Any CHD OR (95% CI)	ASD OR (95% CI)	VSD OR (95% CI)
Maternal SLE			
No	Reference	Reference	Reference
Yes	1.46 (0.53–4.04)	2.05 (0.66–6.37)	1.50 (0.28–8.11)
Sex			
Male	Reference	Reference	Reference
Female	0.88 (0.49–1.57)	0.77 (0.36–1.62)	0.98 (0.37–2.66)
Education			
≤ High school	Reference	Reference	Reference
≥ College	0.87 (0.45–1.68)	1.07 (0.47–2.43)	0.96 (0.33–2.78)
Ethnicity			
White	Reference	Reference	Reference
Other	0.57 (0.27–1.18)	0.66 (0.28–1.58)	0.60 (0.19–1.93)
Pregestational diabetes mellitus			
No	Reference	Reference	Reference
Yes	2.99 (0.96–9.29)	3.72 (0.99–14.00)	4.43 (0.85–23.14)
Gestational diabetes mellitus			
No	Reference	Reference	Reference
Yes	2.23 (0.76–6.55)	1.68 (0.38–7.46)	5.32 (1.40–20.12)
Corticosteroids			
No	Reference	Reference	Reference
Yes	5.65 (1.65–19.34)	3.26 (0.68–15.75)	3.73 (0.43–32.54)
Antimalarials			
No	Reference	Reference	Reference
Yes	0.29 (0.01–5.30)	–	0.60 (0.02–19.96)
Immunosuppressives			
No	Reference	Reference	Reference
Yes	1.77 (0.09–35.98)	–	–
Antidepressants			
No	Reference	Reference	3.29 (0.08–132.49)
Yes	1.12 (0.25–4.92)	0.98 (0.13–7.60)	Reference
Hypertension			
No	Reference	Reference	Reference
Yes	0.36 (0.04–3.43)	0.62 (0.06–6.02)	–
Asthma			
No	Reference	Reference	Reference
Yes	1.79 (0.63–5.04)	0.46 (0.06–3.72)	1.76 (0.32–9.60)

ASD indicates atrial septal defect; CHD, congenital heart defect; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

Table 6. Frequency of Congenital Heart Defects With and Without Repair Procedures Among SLE Offspring and Control Children (n=9212) in Quebec's Administrative Databases, Canada, 1989 to 2009

Types	SLE Offspring (n=719)	Control Children (n=8493)	*P* Values
CHDs, n (%)			
All CHDs	37 (5.1)	159 (1.9)	<0.0001
CHDs with repair procedures	4 (0.6)	6 (0.1)	0.005
ASDs, n (%)			
All ASDs	21 (2.9)	68 (0.8)	<0.0001
ASDs with repair procedures	2 (0.3)	3 (0.0)	0.052
VSDs, n (%)			
All VSDs	12 (1.7)	56 (0.7)	0.002
VSDs with repair procedures	1 (0.1)	2 (0.0)	0.22
Cardiac valve anomalies, n (%)			
All valve anomalies	7 (1.0)	26 (0.3)	0.009
Valve anomalies with repair procedures	0 (0)	0 (0)	–

ASD indicates atrial septal defect; CHD, congenital heart defect; SLE, systemic lupus erythematosus; and VSD, ventricular septal defect.

excluding children who had ≥1 fetal echocardiography, the effect estimates for all types and subtypes of CHD were similar in comparison with the overall analysis results. However, this sensitivity analysis did not account for subtle forms of detection bias that might have occurred after delivery. Indeed, mothers with SLE might be more concerned that their child develops a health problem than control mothers, and they might seek medical attention for their offspring more frequently. If this were the case, it would increase the number of CHD cases diagnosed in children born to SLE mothers, particularly minor and asymptomatic cases. To strengthen our case, we found a substantially increased risk of CHD repair procedures in offspring of SLE mothers in comparison with controls, which does not suggest that detection bias occurring after the pregnancy solely explained the observed association between CHD and maternal SLE.

Our study has some potential limitations. As mentioned previously, the subsample analysis accounting for relevant medication exposures did not allow us to precisely estimate the association between maternal SLE and CHD in offspring because of the limited power given by the reduced sample of subjects with provincial drug coverage. Regardless, this is the largest study to date assessing the risk of CHD in SLE offspring.

Another potential limitation is that medication exposures were defined based on filled prescriptions, which might not have reflected actual intake. However, it is likely that most women who filled a prescription for a specific medication took at least 1 dose, because, within the RAMQ prescription plan, beneficiaries need to cover part of their medication cost.[29]

In addition, in all observational studies, unmeasured or poorly measured confounding represents a major concern. We have considered this and used well-defined proxies for certain variables (eg, socioeconomic status, race/ethnicity). Still, administrative databases do not contain information on, for example, smoking, obesity, or alcohol use, which have all been associated with an increased risk of having a child with CHD in exposed pregnant women. However, previous data from Quebec suggest that smoking practices, obesity prevalence, and alcohol use in SLE patients are comparable to the general population.[30] Therefore, the lack of information on these variables is unlikely to have introduced substantial bias.

Other limitations include our inability to adjust for folic acid and multivitamin exposures during pregnancy, because these supplements are frequently obtained without a prescription (ie, over the counter), and thus not captured in a large proportion of women covered by the RAMQ-Rx plan. Moreover, stillbirths were not included a priori in our analyses because a significant proportion of stillbirths in Quebec result from pregnancy

termination, for which no information on the outcome of interest is recorded.[15] Still, in our cohort, we observed few stillbirths resulting from pregnancy termination, and the effect estimate for CHD did not change when stillbirths were included in the overall analysis (see online-only Data Supplement).

Furthermore, Quebec's administrative databases do not record serological data on any individual. This would have been of interest particularly in women with SLE to determine if specific types of maternal autoantibodies, such as anti-Ro/SSA and antiphospholipid antibodies, predict CHD in children born to women with SLE. Still, establishing an association between in utero SLE exposure and CHD shed new light on the potential role of maternal autoantibodies and cytokines in CHD pathogenesis.

Indeed, maternal SLE-related mechanisms that could be implicated in the physiopathology of CHD in offspring include autoantibody-mediated damage and cytokine imbalance. Transplacental transfer of maternal IgG antibodies begins in the second trimester, reaching circulating levels in the newborn that exceed maternal levels, owing to active transport across the placenta.[31] Anti-SSA/Ro and anti-SSB/La antibodies, found in ≈40% of women with SLE, cross the placenta and are associated with the development of neonatal lupus, with congenital heart block being the most characteristic cardiac manifestation. Investigators have demonstrated that maternal anti-SSA/Ro and anti-SSB/La antibodies bind apoptotic fetal cardiocytes, resulting in the release of proinflammatory and profibrosing cytokines, and ultimately scarring.[32] This process likely extends beyond the conduction tissue, involving the myocardium, endocardium, and valves. In a recent retrospective analysis of autopsies from 18 cardiac neonatal lupus cases, cardiac histological damage outside the conduction system was frequently observed.[12] In particular, 1 autopsy showed a lymphohistiocytic infiltrate with inflammatory giant cells in the ventricular septum, whereas another displayed foci of microscopic calcification in the atrial septum. Moreover, 40% (6/15) of deaths attributable to congenital heart block had pathology findings such as fibrosis and calcification of the valves and valve apparatus, including the tricuspid, mitral, aortic, and pulmonary valves.[12]

Cardiac septation occurs early in embryogenesis and is complete by 6 weeks of gestation.[33] Because transplacental passage of maternal autoantibodies only occurs as early as the 20th week of gestation, it is unlikely that maternal autoantibodies directly interfere with cardiac septation. However, muscular VSDs, which account for ≈75% of all VSDs, are thought to arise from foci of cellular death that occur during active cardiac remodeling, within an already formed ventricular septum.[34] In addition, maternal autoantibodies might prevent closure of cardiac septal defects that might have closed otherwise, possibly explaining the excess risk of cardiac septal defects in offspring of SLE mothers in comparison with controls.

Antiphospholipid antibodies (aPLs) are another type of autoantibodies commonly found in women with SLE, which also cross the placenta. In a recent study of children born to women with antiphospholipid syndrome, 40% of neonates had positive aPL in cord blood.[35] aPLs are strongly associated with valvular disease (eg, valvular nodules, regurgitation, and verrucous endocarditis) in aPL-positive adult patients with and without SLE.[36] Valvular deposits of aPLs in affected adult subjects are thought to play an important pathogenic role in valvular disease.[36] Although previous studies have reported perinatal thrombotic events occurring in children born to aPL-positive mothers, there are currently no data on the prevalence of congenital valve anomalies or other types of CHDs in these children.[37] Because aPLs are involved in valvular damage in seropositive adult subjects and cross the placenta, it could be hypothesized that they may play a role in valve anomalies in exposed fetuses.

Cytokines, such as transforming growth factor beta (TGF-β), play an important role in cardiac embryogenesis. In particular, adequate endocardial cushion formation, which is a critical step in cardiac septation, requires expression of TGF-β.[38] The importance of both maternal and fetal TGF-β in cardiac embryogenesis has been well illustrated in animal models.[38] Notably, TGF-β-1–null mice, born to TGF-β-1–null mothers, demonstrate severe CHD, whereas TGF-β-1–null mice born to wild-type mothers (ie, with normal expression of TGF-β-1) do not. Because transplacental transfer of circulating TGF-β can occur from mother to fetus, investigators hypothesized that maternal TGF-β-1 might rescue any potential heart defects in the null offspring.[38] Interestingly, in SLE patients, serum levels of TGF-β-1 are substantially lower than in controls, with levels inversely correlating with disease activity.[39] Thus, maternal TGF-β rescue of fetuses with defective TGF-β levels might not occur in women with SLE, potentially accounting for the increased risk of CHD.

In conclusion, children born to women with SLE have an increased risk of CHD, including a specifically increased risk of ASD, VSD, and valve anomalies, in comparison with children from the general population. In addition, offspring of SLE mothers have substantially increased odds of CHD repair procedures in comparison with children from the general population. Our findings prompt further research to elucidate the potential role of disease-related factors, such as in utero drug exposures, maternal autoantibodies and cytokines, which might explain the increased likelihood of CHD in children born to mothers with SLE.

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Disclosures

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CLINICAL PERSPECTIVE

A handful of uncontrolled observational studies have suggested a potentially increased prevalence of congenital heart defects (CHDs) in the offspring of mothers with systemic lupus erythematosus (SLE). Thus, we aimed, in a large population-based study, to determine whether children born to women with SLE have an increased risk of CHD in comparison with children born to women without SLE. In addition, we aimed to determine whether offspring of SLE mothers have an increased risk of particular CHD subtypes, including atrial septal defects, ventricular septal defects, and valve anomalies, in comparison with offspring born to unaffected mothers. The Offspring of SLE Mothers Registry (OSLER) includes 719 children born to mothers after a diagnosis of SLE and a control group of 8493 children born to mothers without SLE. We ascertained CHD based on ≥1 hospitalization or physician visit with relevant diagnostic codes, within the first 12 months of life. Within the largest cohort of SLE offspring ever assembled, we observed that children born to SLE mothers had a >2-fold increase in the risk of CHD, and specifically a >2-fold increase in the risk of certain CHD subtypes, including atrial septal defects, ventricular septal defects, and valve anomalies, in comparison with children from the general population. In addition, in comparison with the general population, we found that offspring of SLE mothers had a substantially increased risk of CHD repair procedures than children from the general population. Our hypothesis-generating data provide a new direction for additional studies of maternal autoimmunity and CHD risk.

SUPPLEMENTAL MATERIAL

Title: Increased Congenital Heart Defects in Children Born to Women with Systemic Lupus Erythematosus: Results from the Offspring of Systemic Lupus Erythematosus Registry Study

Authors: Évelyne Vinet[1,2], MD; Christian A. Pineau[2], MD; Susan Scott[1], MSc; Ann E. Clarke[1,3], MD, MSc; Robert W. Platt[4], PhD; Sasha Bernatsky[1,2], MD, PhD.

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Supplemental Methods

For this study, we worked in collaboration with the "Régie de l'Assurance Maladie du Québec (RAMQ)" which manages both the MED-ECHO and physician billing databases. The RAMQ employs skilled data analysts, who extracted the data, according to our pre-specified requirements, to create the exact dataset needed for our study. Only information judged useful for the conduct of the study was transmitted to the research team, as data managed by the RAMQ is highly restricted by the "Commission d'accès à l'information du Québec". Therefore, we only had access to the cohort once it was created. We verified that the cohort conformed to our selection criteria (i.e. appropriate SLE case definition, matching with controls, etc). However, we do not have information on women who were not included in our study and could not produce a flow diagram illustrating the subject selection from the source population.

Stillbirths were not included in our analyses because a significant proportion of stillbirths in Quebec result from pregnancy termination, for which no information on the outcome of interest is recorded. In Quebec, information on stillbirths are recorded based on the following definition: death prior to the complete expulsion or extraction from its mother of a product of conception weighing 500 or more grams, regardless of the gestational age. Since pregnancy terminations are performed up to 24 weeks of gestation in Quebec, some fetal deaths are labeled as stillbirths even if they result from a pregnancy termination.

In a matched cohort study, ignoring the matching variables can leave bias if there are additional confounders, even when controlling for these additional confounders.

Therefore, control for the matching variables is needed when dealing with matched cohort data, although a matched analysis per se is not required.[1]

Models estimated with generalized estimating equations account for the correlation in outcomes of children born to the same mother (i.e. the probability of a congenital anomaly is higher when a sibling has been affected), with each mother serving as the clustering unit.[2]

Multiple imputation was performed assuming an arbitrary missing pattern, using a multivariable normal approach via the Markov chain Monte Carlo method, and included the same covariates as the primary multivariable model. Multivariable analysis results were very similar using either the dataset with missing data or the imputed dataset.

We compared means between SLE offspring and control children with a t-test and proportions with a chi-square test, unless cells were too sparse, in which case we used a two-sided Fisher's exact test.

Results

There were 10 stillbirths among 729 SLE births (1.4%, 95% CI 0.7, 2.6) and 49 stillbirths among 8542 control births (0.6%, 95% CI 0.4, 0.8). For all stillbirths, cause of death was identified in the mandatory stillbirth report form. In the SLE group, one stillbirth was due to pregnancy termination, while no stillbirth was attributed to CHD. In the control group, two stillbirths were due to pregnancy terminations, while one stillbirth was attributed to CHD. The effect estimate for CHD did not change when we included stillbirths in the overall analysis (OR 2.80, 95% CI 1.94, 4.04).

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Table 1S. Diagnostic codes for congenital heart defects

Type of congenital anomaly	ICD*-9 codes	ICD-10 codes
Congenital heart defect	745, 746, 7471-7474	Q20-Q26 excluding Q24.6, Q25.0
Ventricular septal defect	7454	Q210
Atrial septal defect	7455	Q211
Cardiac valve anomaly	746.0-746.6	Q22, Q23

*International Classification of Diseases (ICD)

Table 2S. Race/ethnicity definitions

Race/Ethnicity	Definition
Caucasian	If both maternal and paternal birthplaces are in Canada, United States, or Europe (excluding Spain) with language at home and maternal language being English, French, or another language spoken in Europe (excluding Spanish)
Other	If both maternal and paternal birthplaces are not in Canada, United States, nor Europe (excluding Spain) and/or If language at home and maternal language is not English, French, or another language spoken in Europe (excluding Spanish)

Table 3S. Repair procedure codes

Type of congenital anomaly	Repair procedure codes*
Congenital heart defects	47.01-47.97
Cardiac septal defects	47.51-47.55, 47.61-47.64, 47.71-47.74, 47.95
Cardiac valve anomalies	47.01-47.29, 47.96, 47.97

*Reference: Classification canadienne des actes diagnostiques, thérapeutiques, et chirurgicaux. Institut canadien d'information sur la santé - CCI. 2004. http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=codingclass_cci_f (last accessed March 4th, 2014)

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