THE IMPACT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ON OBSTETRIC OUTCOMES AND INFECTION SUSCEPTIBILITY AMONG INFANTS BORN TO WOMEN WITH SLE

By

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Kitaw Demissie, MD, PhD and Stephan Schwander, MD, PhD

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ABSTRACT OF THE DISSERTATION

The Impact of Systemic Lupus Erythematosus (SLE) on Obstetric Outcomes and Infection Susceptibility Among Infants Born to Women with SLE

By DENISE ELSASSER DIETZ

Dissertation Directors:

Kitaw Demissie, MD, PhD and Stephan Schwander, MD, PhD

Context: Understanding the obstetric outcomes in women with Systemic Lupus Erythematosus (SLE) continues to be an important area of research. Furthermore, understanding its impact on the fetal immune system is an emerging area of interest. **Specific Aims:** The specific aims of this dissertation were to 1) examine the obstetric outcomes of women with SLE in comparison to women without SLE in the United Kingdom (Study 1); and 2) to investigate whether infants born to women with SLE have a higher risk of infection, or of sepsis, when compared to infants born to women without SLE (study 2). **Design, Setting and Subjects**: The Clinical Research Practice Datalink (CPRD) – Gold, the Hospital Episode Statistics (HES) and Mother-Baby linkage data were used to gather women with SLE enrolled in the database since inception (1987) for studies 1 and 2. The population for study 1 was women who became pregnant after diagnosis with SLE. Live born infants of women with SLE were ascertained as the exposed population in study 2. Women without SLE were utilized as a control group for the retrospective cohort study 1, and infants born to mothers without SLE were used as a control group in the retrospective cohort study 2. **Results**: Study 1 showed an increasing trend of frequency of outcomes among the SLE population. Specifically, the frequency of caesarian section (25.8% vs. 22.5%), preterm birth (9.2% vs. 6.2%), miscarriage (18.7% vs. 16.8%), and stillbirth (0.7% vs. 0.4%) was higher among women with SLE. While most outcomes showed an approximate 15% increase in frequency compared

to women without SLE, preterm birth and stillbirth was 45% increased. After adjustment for maternal age, parity and birthweight, caesarian section remained the only adverse event with an increased risk for women with SLE ([Adjusted Risk Ratio (aRR)] aRR = 1.44, 95%CI: 1.06, 1.97). When stratified by type, women with SLE were at a higher risk of elective caesarian section compared to women without SLE (aRR = 1.90; 95% CI: 1.16, 3.11). Results from study 2 found that 15% of infants born to mothers with SLE had a general practitioner visit for infection in the first two years of life, compared to 12.3% of infants born to born to mothers without SLE (Risk Ratio (RR)= 1.11; 95%CI: 1.0, 1.4). Estimates adjusting for preterm birth and maternal age were similar (aRR = 1.24, 95% CI: 0.94, 1.62). The specific infection categories showing an increased risk in adjusted models were "other urinary tract infections" (aRR = 2.29; 95%CI: 1.00, 5.25) and "other bacterial infections" (aRR = 3.29; 95%CI: 1.00, 10.86). There was insufficient data to examine risk by time period. Infants of mothers with SLE were not at an increased risk for hospitalization due to infection or sepsis. **Conclusion**: Women with SLE are able to have successful pregnancy outcomes but are at higher risk for caesarian section (study 1). Infants to mothers with SLE do not appear to be at increased risk of infection overall but may be at a small increased risk of UTI and other bacterial infections (study 2). Further research is needed to clarify these associations.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which targets tissues and organs. It is associated with the production of autoantibodies to macromolecules, most notably those within the cell nucleus (Pisetsky, 2019). This high production of autoantibodies forms complexes which deposit into tissue and organs and cause inflammation (Pisetsky, 2019). This inflammation may lead to tissue damage. The clinical manifestations of SLE are highly variable and may include fatigue, loss of appetite, weight loss, and joint pain (Lisnevskaia, 2014; Kaul, 2016). SLE may also affect different organ systems including the respiratory system, central nervous system, hematopoietic system and the renal system. Studies suggest that women with SLE are at higher risk for pregnancy complications such as fetal loss, preterm birth, and preeclampsia (Vinet, 2012; Clowse, 2005; Clowse, 2008). A population-based study of 1,334 women in a Quebec administrative database found a standardized incidence ratio of 0.79 (95% CI = 0.73-0.86) when comparing SLE live born to that of the general population (Vinet, 2012). An increased risk of fetal loss may be strictly associated with high lupus activity (i.e. flare). Lupus activity is determined clinically by a physician and involves a measurable increase in disease activity in one or more organ systems involving new or worsened clinical signs and symptoms and/or laboratory measurements. Lupus activity must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment (Ruperto, 2011). A 2006 study of the Hopkins Lupus Cohort found that high lupus activity during pregnancy was associated with preterm birth and fewer live births; however, data regarding live births was not statistically significant ($p = 0.063$) (Clowse 2005). A United States study using the National Inpatient Sample reported that caesarean section (OR = 1.7), preterm labor (OR = 2.4) and preeclampsia (OR = 3.0) were more likely in women with SLE (Clowse 2008).

SLE diagnosis can be difficult because the symptoms of SLE are diverse; it is estimated that diagnosis of SLE in adults can be as long as two years after onset (Cervera, 1993). The impact of adverse events for a pregnant woman with SLE has not extensively been researched in a longitudinal database.

Research has shown that women with the autoimmune disease SLE are at higher risk for infection than women without SLE (Danza, 2013). Furthermore, mouse and human studies have found an association between high levels of autoantibodies and impairment of neurological fetal development (Vinet, 2015; Neri, 2004). Given that the fetal immune system is developing in an immune compromised environment, coupled with the increased maternal risk of infection it may be postulated that the mother's weakened immunity in conjunction with the development of the fetal immune system in less optimal environment predisposes a young child to a higher risk of infection. This thesis utilizes infection and sepsis events as clinical manifestations of deficiencies in the development of the fetal immune system. Only two studies have been identified testing this hypothesis. In a Swedish study of SLE patients and their offspring, SLE during pregnancy was associated with increased risk of infections in infants aged 0-2 years requiring hospitalization. The focus of the Swedish study was to describe the pregnancy and postpartum experience in SLE and pre-SLE in context with background risks from the general population with infant infection as one outcome. The Swedish study found that 21% of infants born to mothers with SLE during pregnancy had an infection during their first year of life compared with 25% of infants born to mothers pre-SLE diagnosis and 14% of the general population of infants (Arkema, 2016). While a specific mechanism was not discussed, the increased frequency of pre-SLE diagnosis caused the authors to suggest that infant infection may be associated with an altered maternal immunological profile that occurs before clinical symptoms appear (or are clinically able to be accurately diagnosed). A more recent study found an increased risk of infection and sepsis among infants born to women with SLE within the first 30 days of life (Ignacio, 2018). While a specific mechanism was not

discussed, the authors concluded that the observation was largely, though not solely, due to preterm birth.

Data regarding pregnancy-related outcomes in women with SLE are not available for the United Kingdom (UK) and there is a need to further describe obstetric outcomes of women with SLE. The Clinical Practice Research Datalink (CPRD) was utilized to assess outcomes during pregnancy among the SLE population. This thesis addressed the association of SLE during pregnancy with several outcomes (i.e. abruptio placentae, caesarean section, stillbirth, pre- eclampsia, preterm birth, miscarriage, and termination) and stratified SLE patients based on clinical disease involving organ systems. Medication use among SLE patients was also explored.

My research project and this thesis address the topics of obstetric outcomes and increased risk of infection in the offspring and generates information that may help with family planning discussions and support the obstetric care of an SLE patient and infants born to mothers with SLE.

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OBSTETRIC OUTCOMES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITHIN THE CLINICAL PRACTICE RESEARCH DATALINK

By

DENISE ELSASSER DIETZ

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ABSTRACT OF MANUSCRIPT 1 OF 2

Obstetric Outcomes In Women With Systemic Lupus Erythematosus Within The Clinical Practice Research Datalink

By DENISE ELSASSER DIETZ

Dissertation Directors:

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Objectives: There is currently limited data on maternal and infant outcomes of pregnancy women with Systemic Lupus Erythematosus (SLE). This thesis addressed the association of SLE during pregnancy with several maternal and infant outcomes: abruptio placentae, caesarean section, stillbirth, pre-eclampsia, preterm birth, miscarriage, and elective termination. In addition to assessing outcomes compared to the healthy population, outcomes were stratified by organ involvement and the subcategory of kidney involvement. Medication use during pregnancy and 1-year prior to pregnancy was also investigated. **Methods**: A retrospective cohort study was designed using the Clinical Practice Research Datalink during the time period of January 1987-July 2018. Women with SLE and a subsequent pregnancy were identified and matched to healthy women in a 1:4 ratio by age and year of pregnancy index date. Frequency of outcomes, risk ratios and 95% confidence intervals were reported. **Results**: The frequency of caesarian section (25.8% vs. 22.5%), preterm birth (9.2% vs. 6.2%), miscarriage (18.7% vs. 16.8%), and stillbirth (0.7% vs. 0.4%) were higher among women with SLE. The frequency of elective termination among SLE patients versus women without SLE was 8.5% and 8.9%, respectively. The frequencies of the adverse outcomes of interest among women without SLE were as follows were within the range reported by the NHS for the UK general population. Women with SLE were at increased risk of

caesarian section after adjustment for maternal age, parity, body mass index (BMI) and birthweight (RR = 1.44; 95% CI: 1.06, 1.97; $p<0.05$). The risk did not increase further when risk was analyzed by organ involvement category. **Conclusion**: Findings suggest that women with SLE can have successful pregnancies and outcomes but are at higher risk of caesarian section.

OBSTETRIC OUTCOMES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITHIN THE CLINICAL PRACTICE RESEARCH DATALINK

INTRODUCTION

Systemic Lupus Erythematosus, (SLE) an autoimmune disease which may involve multiple organ systems, is known to be more common among women than men (Chakaravarty, 2007; Naleway, 2005; Mccarthy, 1995) with diagnosis peaking in the childbearing years (Somers, 2014). The incidence of SLE in resource-rich countries is approximately 1-25 per 100,000 person-years (Guillermo, 2010; Rus, 2002) with a reported incidence of 4.0 per 100,000 person-years in the United Kingdom (Somers, 2007; Nightingale, 2007; Rees, 2016). Each year, approximately 3,400 women (<0.01% of all births) with SLE give birth in the US (Clowse, 2008). While the fertility rate among patients with SLE appears to be comparable to the general population, earlier studies have suggested that women with SLE tend to have smaller families (Hardy, 1999; Lateef, 2012; Petri, 1992).

Studies suggest that women with SLE are at higher risk for complications such as fetal loss, preterm birth, and preeclampsia compared to women without SLE. A population-based study of 1,334 women in Quebec administrative databases Med-Echo and Régie de l'assurance maladie du Québec (RAMQ) found a standardized incidence ratio of 0.79 (95% CI = 0.73-0.86) when comparing SLE live births to that of the general population (Vinet, 2011). US National Inpatient Sample data found that women with lupus had higher risks of caesarian section (OR = 1.7), preterm labor (OR = 2.4) and preeclampsia (OR = 3.0) (Clowse, 2008) than women without SLE. A large meta-analysis, which included 2,751 pregnant women with SLE and lupus nephritis (LN), identified high maternal complication rates

and an overall maternal mortality rate of 1% (Smyth, 2010). These studies did not provide descriptive details regarding patient medication use.

The impact of adverse events for a pregnant woman with SLE has not extensively been researched with respect to medication use. Several medications are utilized for the SLE patient including hydroxychloroquine (HCQ), immunosuppressants, corticosteroids and TNF-α inhibitors. HCQ is the first line medication for SLE and is used for more mild disease (i.e without organ involvement). Based on a study of 257 women using HCQ, discontinuation of the medication before pregnancy may increase the risk for flare during pregnancy (Clowse, 2006). This risk remained elevated (although not statistically significant) when adjusting for year of delivery, age, ethnicity, history of lupus nephritis and antiphospholipid disease. The study found no increased risk of stillbirth ($p = 0.85$), preterm birth ($p=0.87$), or small for gestational age (SGA) ($p=0.93$), however, the authors express that the study was under powered due to small sample size. A recently published study found an association between HCQ, and higher rates of live birth (=0.05) and a lower prevalence of antiphospholipid antibody-related pregnancy morbidity ($p=0.04$) (Sciascia, 2016).

Accepted standards for diagnosing SLE patients are available, such as those put forth by the American College of Rheumatology and the European League Against Rheumatism; UK specific guidelines from the British Society for Rheumatology have recently been released.

Data suggest an association between flares and adverse outcomes. A 2006 study of the Hopkins Lupus Cohort found that high lupus activity (i.e. flare) during pregnancy was associated with preterm birth and fewer live births; however, data regarding live births was not statistically significant ($p = 0.063$) (Clowse, 2007). Studies addressing flares have defined the event differently, making cross study comparison and interpretation difficult. The International Lupus Consensus group put forth this definition in 2010:

> "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor, and usually, there would be at least consideration of a change or an increase in treatment (Ruperto, 2011)."

Data regarding pregnancy related outcomes in women with SLE are not available for the United Kingdom (UK). The Clinical Practice Research Datalink (CPRD) was utilized to assess outcomes during pregnancy among the SLE population. This thesis addressed the association of SLE during pregnancy with several outcomes (i.e. abruptio placentae, caesarean section, stillbirth, pre- eclampsia, preterm birth, miscarriage, and termination) and stratified SLE patients based on clinical disease involving organ systems. Medication use among SLE patients was also explored.

METHODS

The Clinical Practice Research Datalink (CPRD) is a longitudinal database that is representative of the UK population. Records are available from 1987 and comprise patient files from general practitioners within the UK. There is a wealth of information stored in the database including clinical information, diagnosis codes, tests and medications. There are over 12 million individuals and 660 practices contributing data to CPRD. For the current thesis, a retrospective cohort analysis was designed using records from 1987 through the July 2018 data cut. Male patients, patients with less than two years of continuous data, those without up-to-standard/acceptable and eligibility flags were excluded from the population pool. SLE was defined using READ codes: F371000, F396100, H57y400, K01x400, K01x411, Myu7800, N000.00, N000000, N000100, N000200, N000300, N000400, N000600, N000z00 and Nyu4300 (see Appendix 1). The first occurrence of a READ code for SLE was assigned as the SLE index date. Those with a pregnancy subsequent to SLE index date remained among the eligible SLE patient population. Pregnancies were defined per the validated algorithm put forth by Devine et al. (Devine, 2010). Briefly, patient records were checked to verify presence of a valid outcome code. Outcome codes were classified into three categories, (1) stillbirth, (2) loss (spontaneous abortion and termination) and (3) livebirth. Once the first valid outcome was found, subsequent outcome codes were ignored within a 210-day cutoff for categories one and three and a 60-day cutoff for category two. Pregnancy index date was defined as the earliest pregnancy related READ code found within 280 days prior to the outcome date. Using the completed pregnancy profile, the common conditions of hypertension and diabetes were chosen as exclusion criteria because they are known to have adverse outcomes being analyzed in this analysis (i.e.: preeclampsia and stillbirth). The same algorithm for pregnancy and exclusion criteria was applied for patients without SLE (i.e. patients without a READ code for SLE). SLE patients were matched in a 1:4 ratio by age and year of pregnancy index date to those without a READ code for SLE. Patients were only eligible to contribute one pregnancy to the sample

population in order to reduce for correlation for multiple births from the same mother. Non-singleton births were also excluded to reduce the effect of clustering. A flowchart of the sample SLE population is shown in Figure 1.1.

Clinical outcomes of interest were defined according to UK standards and were placental abruption; caesarian section (emergency and elective); miscarriage (fetal loss <24 weeks gestation); elective termination; preterm birth (livebirth <37 weeks gestation) and stillbirth (fetal death and expulsion 24+ weeks gestation). In order to maximize the capture of preterm birth, in addition to READ codes, the variable was also generated using the difference in weeks between the outcome date and index date of pregnancy. If the difference was <37 weeks, the pregnancy was considered preterm.

Statistical Analysis

The frequency, relative risk (RR) and 95 percent confidence interval (95% CI) were reported for these clinical outcomes in the SLE versus women without SLE. Multivariable binomial regression was used in the analysis for the estimation of RR (Robbins, 2002). Adjustments were made for maternal age, parity and birthweight and adjusted risk ratios were calculated. The frequency, RR and 95% CI for clinical outcomes were also stratified by SLE organ involvement. Affirmative organ involvement was classified using READ codes that specified an organ system in the code description (see Appendix 1). The subcategory of nephritis was classified if the organ system was specific to the kidneys. All statistical analysis was done using SAS Enterprise Guide version 6.1.

RESULTS

A total of 283 women with SLE and 1,132 women without SLE were included in this analysis. Demographic data is shown in Table 1.1. The mean age was 32 years (range 17-46 years). The majority of both study populations had a BMI in the normal range (18.5-24.9) and had a parity of 1. Approximately 5% of women in each group smoked during pregnancy.

Among women with SLE (see Table 1.2) the mean duration of disease was 6.7 years (standard deviation 5.6). The majority of women had no noted organ involvement before or during pregnancy. Less than 7% of women with SLE had antiphospholipid syndrome, which is associated with preeclampsia, fetal growth restriction, and stillbirth. A minority of women (less than 8%) were positive for Anti-Sjögren's-syndrome-related antigen A or antigen B (SSa, SSb, respectively) antibodies, which is associated with neonatal lupus and congenital heart block. The Systemic Lupus Activity Measure (SLAM), a scoring system used to measure the severity of disease, is not readily recorded in the medical records and, thus, was not analyzed. A small minority of patients in this SLE cohort used relevant medications (e.g.: hydroxychloroquine (HCQ), corticosteroids, immunosuppressants, heparin and monoclonal antibody anti CD20) during pregnancy and approximately one-fifth of patients used medications within one year before becoming pregnant (Table 1.2). The most utilized medication one year before pregnancy was hydroxychloroquine. HCQ usage was used among 8.8% of patients within one year of pregnancy and dropped to 1.8% of patients using the medication during pregnancy. Number of concordant patients using medication before and during pregnancy for corticosteroids, immunosuppressants and HCQ are 0, 1 and 0, respectively. Thus, all patients discontinued corticosteroids when they became pregnant; one patient continued to use immunosuppressants when she became pregnant; and all patients on HCQ discontinued during pregnancy.

Outcomes of Interest

Outcomes of interest in this analysis were abruption, preeclampsia, preterm birth, miscarriage, caesarian section, elective termination and stillbirth. Frequencies of adverse outcomes of interest (i.e.: abruption, preeclampsia, preterm birth, miscarriage, and stillbirth) among the SLE population were as follows: 0.0%, 0.4%, 9.2%, 18.7%, 0.7%. Frequencies of the adverse outcomes of interest among women without SLE were as follows: 0.2%, 0.8%, 6.2%, 16.8%, 0.4%. An increased risk of caesarian section was seen among SLE patients when adjusted for maternal age, birthweight, BMI and parity (adjusted RR [aRR] = 1.44; 95% CI: 1.06, 1.97). Among 283 SLE patients and 1,132 patients without SLE, 124 (44%) and 602 (53%) experienced a complicated pregnancy (i.e.: any of the outcomes of interest), respectively (RR=0.82; 95% CI: 0.71, 0.95). Table 1.4 displays pregnancy outcomes of interest stratified by SLE status. There were 179 and 632 outcomes of interest (events) observed among 283 patients with SLE and 1,132 patients without SLE, respectively. When comparing SLE patients to women without SLE, the frequencies of caesarian section were 26% (N=73) versus 23% (N=255), respectively. The frequencies of elective termination among SLE patients versus women without SLE were 8.5% (N=24) and 8.9% (N=101), respectively. No other outcomes were statistically different among the two populations, with adjusted relative risks of preeclampsia, preterm birth, miscarriage, stillbirth and elective termination as follows: 0.41 (95%CI: 0.51, 3.21), 1.08 (95%CI: 0.62, 1.89), 0.69 (95%CI: 0.35,1.34), 2.18 (95%CI: 0.21, 22.49), 0.81 (95%CI: 0.26, 2.53), respectively.

Table 1.5 displays outcomes grouped by the presence or absence of organ involvement. Of the 283 SLE patients, 253 (89%) had no organ involvement in their medical record as part of their disease. Of the 30 remaining patients with organ involvement noted, the outcomes of interest (when compared women with no organ involvement noted) were virtually similar with no observed differences. SLE patients with nephritis were further analyzed to determine differences in risk. None were noted; however, sample size was small.

DISCUSSION

This thesis sought to identify the effects of SLE on pregnancy outcomes in the UK. Results from this thesis show an increasing trend of frequency of outcomes among the SLE population. Specifically, the frequency of caesarian section (25.8% vs. 22.5%), preterm birth (9.2% vs. 6.2%), miscarriage (18.7% vs. 16.8%), and stillbirth (0.7% vs. 0.4%) was higher among women with SLE. While most outcomes in SLE patients showed an approximate 15% increase in frequency compared to women without SLE, preterm birth and stillbirth each exhibited over a 45% increase in frequency compared to women without SLE.

Frequencies of all outcomes in both study populations were aligned with the general population estimates put forth by the National Health Service (National Health Statistics, 2018). While the aforementioned outcomes of interest were seen in higher frequencies in SLE patients compared to women without SLE, after adjustment for maternal age, parity and birthweight, caesarian section remained the only adverse event with an increased risk for women with SLE (aRR 1.44, 95%CI: 1.06, 1.97). When stratified by type, women with SLE were at higher risk of elective caesarian compared to women without SLE (aRR = 1.90; 95%CI: 1.16, 3.11). No increased risk was seen when risk was analyzed by organ involvement category. Previous studies have correlated stillbirth with nephritis in SLE patients (Clowse, 2007; de Jesus, 2015); however, our findings did not support this. The sample size was small, however, so no firm conclusions can be made. Based on these findings, women with SLE do not appear to be at higher risk of adverse pregnancy outcomes compared to women without SLE.

Both study populations showed lower smoking rates when compared to the general population. Five percent of SLE patients and women without SLE reported smoking during pregnancy. According to the National Health Service, smoking at delivery in the UK is approximately 10% (National Health Statistics, Abortion Statistics, 2018).

This cohort may have consisted of women with milder forms of SLE. Several factors suggest this. Firstly, the exclusion criteria in this study removed the comorbid conditions of hypertension and diabetes due to their association with poor pregnancy outcomes. These criteria could potentially have restricted the study population to milder cases. Additionally, the study population with SLE had low utilization of medication use within 1 year; low utilization of medication during pregnancy; and had a low diagnoses of organ involvement, suggestive of milder disease. Based on our findings, fewer women utilized medication during pregnancy than during the pre-gestational period (Table 1.3). Among the cohort, 17% of SLE patients took medication 1-year prior to pregnancy. As a sensitivity analysis, an investigation was conducted to understand the frequency of medication among the entire SLE population in CPRD and another database, Humedica (a US based electronic medical record database). Within the 2015 data cut of CPRD, the frequency of medication use among all SLE patients was 13% compared to 15% seen in the 2015 data cut of Humedica. This provided confidence of appropriate medication capture among SLE patients in CPRD. Medication use among SLE patients during pregnancy was seen in approximately 5% of SLE patients in this cohort. The vast majority of patients showed discordant medication use between the two-time periods (one year prior and during pregnancy) within medication class. Overall, the cessation of HCQ and immunosuppressants appeared to be successfully sustained for most patients, possibly due to milder disease. Previous research suggests that compared to pre-pregnancy state, one-third of women with SLE will have similar disease course throughout pregnancy, one-third will have increased severity, and one-third will have decreased severity (Personal Communication, 2017). Thus, no firm conclusions can be made as to the cause of medication reduction. Medication use, however, may be more of a surrogate for disease severity as opposed to a causation factor for adverse outcomes. In a study by Arkema et al., increased adverse obstetric outcomes were seen in the pregnancy prior to SLE diagnosis in addition to the first pregnancy after SLE diagnosis, when

compared to women without SLE (Arkema, 2018). Because this was seen in the pre-SLE-diagnosis pregnancy, it suggests that an increase in adverse obstetric outcomes may not be associated with medication use but with disease. Furthermore, studies of relevant medication during pregnancy have failed to find an association with adverse obstetric outcomes (Ostensen 2006; Weber-Schoendorfer, 2014).

If this thesis indeed explored a cohort of women with milder disease, then the occurrence of mostly mild cases in the database may suggest adherence to physician recommendation to postpone pregnancy until remission. It is also plausible that women who have more severe forms of SLE may choose to delay or cease family planning due to uncomfortable clinical manifestations of more severe forms of disease. Literature does show that women with SLE have higher adverse outcomes. However, studies show that when stratifying by severity, adverse outcomes are associated with increased disease severity (i.e. flares, lupus nephritis and/or organ involvement) (Tedeschi, 2016; Clowse, 2005; Georgiou, 2000; Hayslett, 1980; Mintz, 1986; Clark, 2003; Cortes-Hernandez, 2002). Results from this thesis are in-line with these previous findings. Overall, women with SLE who have milder forms of disease can feel confident in a successful pregnancy. Results from this thesis suggest that women with SLE can have successful pregnancies and outcomes but are at higher risk for caesarian section. When stratified by type, women with SLE are at a higher risk for elective caesarian section. If elective caesarian sections are performed with higher frequency in SLE patients then this may explain the reduced risk of adverse events seen in the study population. Thus, increased frequency of elective caesarian section may mitigate the increased potential of an adverse event and may serve as a protective factor. More research into the risk factors for elective caesarian section in the SLE population is needed to address this hypothesis.

Strengths and Limitations

This is the first population-based study in CPRD observing pregnancy outcomes in the SLE

population. Patients with SLE were sought since the inception of the database (i.e. 1987) thus, all SLE patients meeting inclusion criteria were captured in this study.

Limitations of this study are with respect to ethnicity of the study subjects. Because of the nature of the database, ethnicity status was not available for analysis. It is known that SLE affects non-whites disproportionally higher than whites (Wallace, 2013). The LUMINA (Lupus in Minority Populations: Nature vs. Nurture) study recently reported that African American SLE patients are more likely to have organ system involvement, more active disease, and lower levels of social support compared with white lupus patients (Somers, 2014). While ethnicity is largely underreported in CPRD and a known limitation of the data, data show that overall, the majority of those with a record of ethnicity are White (Nightingale, 2017). Furthermore, census data from the UK show that approximately 90% of the population has a recorded ethnicity of White (Office of National Statistics, 2018). While limitations of the dataset prevent verification, census data and data from Nightingale et al., suggest that our study population may be largely white. If true, this may provide an additional reason why our study population showed lower adverse events than other study populations which may include more non-whites.

Study Conclusions

In conclusion, women with milder forms of SLE can feel confident in a successful pregnancy but are at higher risk for caesarian section.

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TABLES AND FIGURES

Figure 1.1: Schematic of Study Population

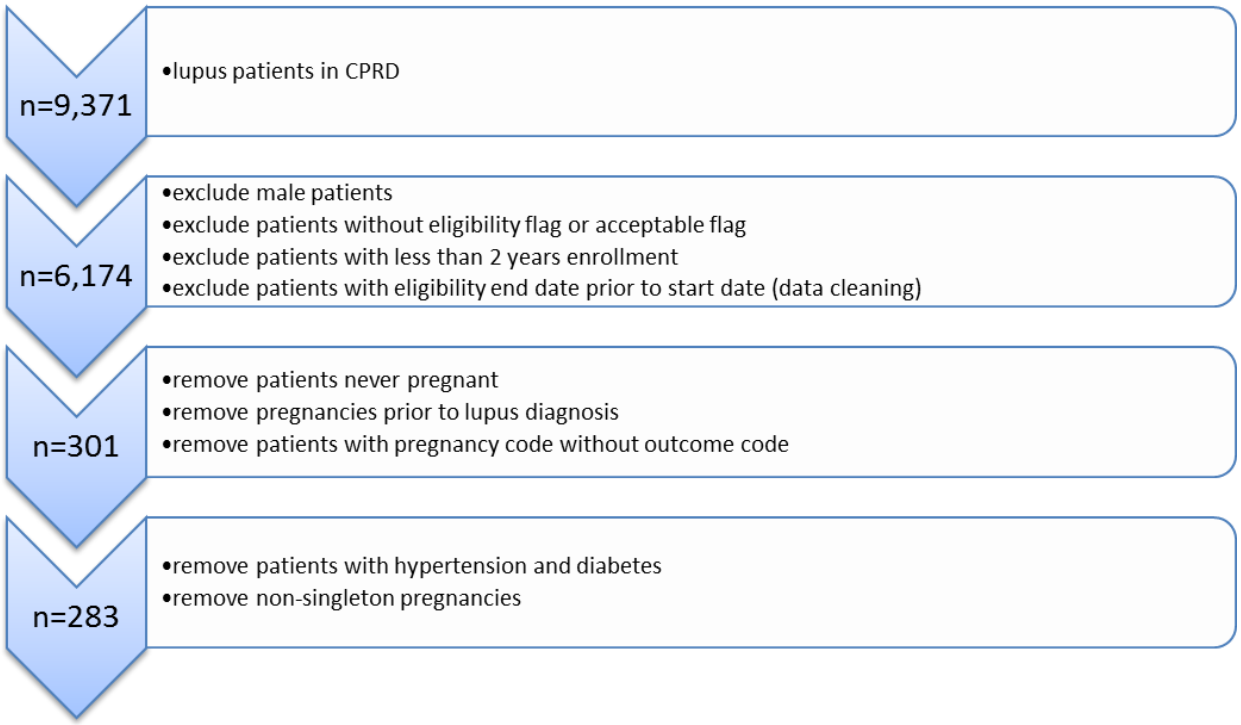

Table 1.1: Baseline Characteristics of the Study Population

Characteristics	Categories	SLE Patients	Women without SLE	p-value
Age at Delivery	N	283	1132	
	Mean (yrs)	32	32	
	Max (yrs)	46	46	
	Min (yrs)	17	17	
BMI n(%)	<18.5	47 (16.6)	195 (17.2)	0.0400
	18.5-24.9	136 (48.1)	453 (40.0)	
	25-29.9	51 (18.0)	187 (16.5)	
	30-39.9	20 (7.1)	136 (12.0)	
	40 and above	2 (0.7)	14 (1.2)	
	Missing	27 (9.5)	147 (13.0)	
Smoking (ever)	No	141 (52.2)	595 (56.3)	0.2299
	Yes	129 (47.8)	462 (43.7)	
Parity n(%)	0	0 (0.0)	2 (0.20)	0.0015
	1	101 (39.9)	512 (50.7)	
	2	63 (24.9)	166 (16.4)	
	3+	88 (34.8)	330 (32.7)	
	Missing	1 (0.4)	0 (0.0)	
Region	East Midland	9 (3.2)	33 (2.9)	0.1605
	East of England	32 (11.3)	89 (7.9)	
	London	51 (18.0)	179 (15.8)	
	North East	2 (0.7)	13 (1.1)	
	North West	27 (9.5)	117 (10.3)	
	Northern Ireland	10 (3.5)	31 (2.7)	
	Scotland	18 (6.34)	60 (5.3)	
	South Central	39 (13.8)	128 (11.3)	
	South East Central	25 (8.8)	106 (9.4)	
	South West	15 (5.3)	107 (9.5)	
	Wales	17 (6.0)	117 (10.3)	
	West Midland	27 (9.5)	120 (10.6)	
	Yorkshire	11 (3.9)	32 (2.8)	
Smoking Status During Pregnancy n(%)	Non-smoker	141 (49.8)	595 (52.6)	0.3781
	Ex-smoker	111 (39.2)	400 (35.3)	
	Smoker	18 (6.34)	62 (5.5)	

Characteristics	Categories	SLE Patients	Women without SLE	p-value
	Missing	13 (4.56)	75 (6.6)	

Table 1.2: Disease Characteristics of Women with Systemic Lupus Erythematosus (SLE)_

Characteristics	SLE Patients (n=283)
Duration of Disease, yrs	
Mean (standard deviation)	6.7 (5.6)
Organ Involvement n(%)	
Organ Involvement Unknown	253 (89.4)
Any Noted Organ involvement	30 (10.6)
Systemic lupus erythematosus with pericarditis	1 (0.3)
Disseminated lupus erythematosus	12 (4.1)
Lupus nephritis	14 (4.8)
Lung disease with systemic lupus erythematosus	2 (0.7)
Nephrotic syndrome in systemic lupus erythematosus	1 (0.3)
Organ Involvement with noted nephritis/nephrotic syndrome	15 (5.3)
Antibody/Antiphospholipid n(%)	
Positive Antiphospholipid Disease Ever before outcome date	20 (7.1)
Positive Antiphospholipid Disease During Pregnancy	5 (1.8)
SLAM score ever before outcome date	1 (0.4)
Ssa Positive Ever before outcome date	21 (7.4)
Ssa Positive During Pregnancy	2 (0.7)
Ssb Positive Ever before outcome date	18 (6.4)
Ssb Positive During Pregnancy	1 (0.4)

SSa = Anti-Sjögren's-syndrome-related antigen A; SSb = Anti-Sjögren's-syndrome-related antigen B

Table 1.3: Medication Use Among SLE Patients During and Prior to Pregnancy

Characteristics	SLE Patients (n=283)
During Pregnancy	**n(%)**
Immunosuppressants During Pregnancy	4 (1.4)
Corticosteroids During Pregnancy	5 (1.8)
Hydroxychloroquine During Pregnancy	5 (1.8)
Heparin	0 (0.0)
Monoclonals	0 (0.0)
1 Year Prior to Pregnancy	
Immunosuppressants One Year Before Pregnancy	12 (4.2)
Corticosteroids One Year Before Pregnancy	9 (3.2)
Hydroxychloroquine One Year Before Pregnancy	25 (8.8)
Heparin	0 (0.0)
Monoclonal Antibody	0 (0.0)

Table 1.4: Number, Frequency and Relative Risk (RR) of Pregnancy Outcomes of Interest Comparing SLE Patients to Women without SLE

Outcome†	SLE Patients (n=283)	Women without SLE (n=1132)	Relative Risk	95% Confidence Interval	Adjusted RR	95% Confidence Interval
	n(%)	**n(%)**				
Total	**179 (63.3)**	**632 (55.8)**				
Abruption	0 (0.0)	2 (0.2)	NR	NR	NR	NR
Caesarian	73 (25.8)	255 (22.5)	1.14	0.91, 1.43	1.44[a‡]	1.06, 1.97
elective	46 (16.6)	167 (14.8)	1.13	0.84, 1.51	1.90[a‡]	1.16, 3.11
emergency	27 (9.5)	96 (8.5)	1.13	0.75, 1.69	1.27[a]	0.75, 2.17
Preeclampsia	1 (0.4)	9 (0.8)	0.44	0.06, 3.49	0.41[c]	0.51, 3.21
Preterm Birth	26 (9.2)	70 (6.2)	1.49	0.97, 2.29	1.06[a]	0.59, 1.89
Miscarriage	53 (18.7)	190 (16.8)	1.12	0.85, 1.47	0.72[a]	0.37, 1.43
Stillbirth	2 (0.7)	5 (0.4)	1.60	0.31, 8.20	1.50[a]	0.16, 14.41
Termination	24 (8.5)	101 (8.9)	0.95	0.62, 1.45	0.81[a]	0.26, 2.57
				Point Estimate		
Birth Weight				0.90	0.87 – 0.93‡	

† = non-mutually exclusive; NR = not reported; ‡=p<0.05
a = adjusted for maternal age, parity, BMI and birthweight; b = adjusted for birthweight and parity; c = adjusted for maternal age and parity

Table 1.5: Number, Frequency and Relative Risk (RR) of Pregnancy Outcomes of Interest Comparing SLE Organ Involvement to those With Organ Involvement Unknown (referent)

	Any Noted Organ Involvement (n=30)		Nephritis (n=15)		Organ Involvement Unknown (n=253)
Outcome†	**N(%)**	**RR (95%CI)**	**N(%)**	**RR (95%CI)**	
Caesarian	6 (20.0)	0.8 (0.4,1.6)	4 (26.7)	1.0 (0.4,2.4)	67 (26.5)
Elective	3 (10.0)	0.6 (0.2,1.7)	2 (13.3)	0.8 (0.2,2.9)	43 (17.4)
Emergency	3 (10.0)	1.1 (0.3,3.3)	2 (13.3)	1.4 (0.4,5.4)	24 (9.5)
Preeclampsia	0 (0.0)	NR	0 (0.0)	NR	1 (0.4)
Preterm Birth	3 (10.0)	1.1 (0.4,3.4)	3 (20.0)	2.2 (0.7,6.5)	23 (9.1)
Miscarriage	9 (30.0)	1.7 (0.9,3.2)	3 (20.0)	1.1 (0.4,3.3)	44 (17.4)
Stillbirth	0 (0.0)	NR	0 (0.0)	NR	2 (0.8)
Termination	4 (13.3)	1.7 (0.6,4.6)	2 (13.3)	1.7 (0.4,6.6)	20 (7.9)

	Any Noted Organ Involvement (n=30)		Nephritis (n=15)		Organ Involvement Unknown (n=253)
Outcome†	**N(%)**	**RR (95%CI)**	**N(%)**	**RR (95%CI)**	

CI = confidence interval; NR = not reported, † = non-mutually exclusive;

ASSESSING THE RISK OF INFECTION AMONG BABIES BORN TO MOTHERS WITH SYSTEMIC LUPUS ERYTHEMATOSUS; A STUDY OF THE FIRST TWO YEARS OF LIFE.

By

DENISE ELSASSER DIETZ

Manuscript 2 of 2 of a dissertation entitled

THE IMPACT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ON OBSTETRIC OUTCOMES AND INFECTION SUSCEPTIBILITY IN INFANTS BORN TO WOMEN WITH SLE

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School of Public Health

and the

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For the degree of

Doctor of Philosophy

Written under the direction of

Kitaw Demissie, MD, PhD and Stephan Schwander MD, PhD

ABSTRACT OF MANUSCRIPT 2 OF 2

ASSESSING THE RISK OF INFECTION AMONG BABIES BORN TO MOTHERS WITH SYSTEMIC LUPUS ERYTHEMATOSUS; A STUDY OF THE FIRST TWO YEARS OF LIFE.

By DENISE ELSASSER DIETZ

Dissertation Directors:

Kitaw Demissie, MD, PhD and Stephan Schwander, MD, PhD

Objectives: To assess whether the offspring of women with SLE are at higher risk of infection and sepsis during the neonatal period, 29 days – 6 months, and six months and older through two years of age. **Methods**: A retrospective cohort study was designed using the Clinical Practice Research Datalink (CPRD) during the time period of January 1987-July 2018. Offspring born to women with SLE were identified and matched to infants born to women without SLE in a 1:4 ratio by year of birth and maternal age. The mother / baby datalink was used to verify maternity. The Clinical Practice Research Datalink – Gold (CPRD-Gold) database was utilized for infection and sepsis in the general practitioner setting. Health Episode Statistics data was also utilized to obtain the number of infection and sepsis events and assess the risk severe enough to warrant hospitalization. Frequencies of outcomes, risk ratios and 95% confidence intervals were reported. **Results**: 15.0% of infants born to mothers with SLE had a general practitioner visit for infection in the first two years of life, compared to 12.3% of infants born to born to mothers without SLE (Risk Ratio (RR)= 1.11; 95%CI: 1.0, 1.4). Estimates adjusting for preterm birth and maternal age were similar ([Adjusted RR] aRR = 1.24, 95% CI: 0.94, 1.62). The specific infection categories showing an increased risk in adjusted models were “other urinary tract infections” (aRR = 2.29; 95%CI: 1.00, 5.25) and “other bacterial infections” (aRR = 3.29; 95%CI: 1.00, 10.86). There

was insufficient data to examine risk by time period. Infants of mothers with SLE were not at an increased risk for hospitalization due to infection or sepsis. **Conclusion**: Infants to mothers with SLE do not appear to be at increased risk of infection overall but may be at a small increased risk of urinary tract infection (UTI) and other bacterial infections. Further research is needed to clarify these associations.

Assessing the risk of infection among infants born to mothers with Systemic Lupus Erythematosus; a study of the first two years of life.

INTRODUCTION

The fetal immune system begins to develop in the weeks following a successful implantation of an embryo in the uterus. By nine weeks of gestation, fetal B-lymphocytes develop in the liver and at 14 weeks of gestation, T-lymphocytes are released from the thymus (Hayward, 1983). Antigen presenting cells are functional by the 12th week of gestation making an adaptive immune response possible by the end of the first trimester. After an infant is born, the immune system maturation is largely influenced by gastrointestinal tract maturation (i.e. bacterial colonization) and oral feeding (Gleeson, 2004; Szczawinsk-Poplonyk, 2012).

The neonatal immune system is considered "immature" largely due to deficiencies in B-cell function and antibody production. The impaired responses are not restricted to adaptive responses alone as functional deficiencies in the immature immune system extend to barriers (i.e. skin), cell population and the complement system.

Research on neonate skin and mucosal immune systems, myeloid and innate lymphoid cells of the immune system, and the complement system reveal continued maturation of the immune system post-partum (Georgountzou, 2017). For example, research has identified that during the first years of life, the skin of full-term neonates continues development of structural and functional components. Illustrations of this include, increasing thickness of skin layers, increasing stratum corneum hydration and a decrease from a more basic skin surface pH of 6.1 – 7.5 to a more acidic 4.5 – 6.7. (Stamatas, 2011). Skin structure develops into adulthood, while shifts in microbiota, pH and water handling properties develop through childhood into adolescence. Gastrointestinal immune components including membrane closure, epithelial growth and antimicrobial proteins, and respiratory system immune functions such as mucociliary clearance and alveolar macrophage function develop in neonates

through childhood. Blood cells and soluble factors also continue development; innate cell quantities will develop through adolescence while neutrophil, natural killer cells, antigen presenting cell functions, toll-like receptor signaling, and complement system will also develop through childhood (Georgountzou, 2017).

Research on cellular differences between neonates and adults reveals several variances (Levy, 2005; Wynn, 2010; Dowling, 2014; Velilla, 2006; De Kleer, 2014; Basha, 2014; Marodi, 2006; Strunk, 2011; Goenka, 2015). For example, granulocytes (neutrophils) have shown quantitative changes throughout the neonatal period, declining post-partum before stabilizing throughout early childhood (Manroe, 1979; Schmutz, 2008). Neonatal immune system impairments are noted in phagocytosis and bactericidal activity within neutrophils and macrophages (Yost, 2009). Neonatal leukocytes show decreased responsiveness and cytokines responses are often T-cell helper2 or T-cell helper 17-polarized (Adkins, 2004). While data specifying age of maturation for toll-like receptors (TLRs), is not available, research on TLRs reveal immune maturity differs between neonates and adults. Research in countries worldwide have been conducted among various culture systems and receptor pathways. A review of conclusions has revealed conflicting results in the study of TLR maturation that varied depending on research methods and techniques applied. Studies including children older than 24 months have focused on the maturation of the TLR4 pathway and show immaturity in comparison to the adult (Levy, 2005; Wynn, 2010; Kollmann, 2009). Two studies evaluate additional TLR pathways up to the age of five (Tulic, 2011; Marr, 2014). Further development would aid in understanding maturation of TLRs among the infant to adult timeline. Complement proteins also reveal dissimilarity; complement proteins C2, C3, C4 and C6 do not appear to reach adult levels until three to six months of age (Drossou, 1995; Wolach, 1997; Ballow, 1974). Complement proteins C8 and C9 are most significantly reduced at birth (Wolach, 1997; Ballow, 1974), and C1q levels do not rise to adult levels until between 18-21 months old (Davis, 1979; de Paula, 2003).

It is established that the maternal state impacts fetal development (DiPietro, 2004). Maternal breastmilk and prepared formula provide a young child with additional immunoglobulin (Ig) immune support such as IgA, and IgG following transplacental transport of *immunoglobulins in utero*. (Camacho-Gonzalez A, 2013). Research among infants born to transplant recipients who utilized immunosuppressants found that they may cause natural-killer cell depletion and B- and/or T-cell depletion (Kozlowska-Boszko, 1997; Motta, 2007). For women with SLE, it had been suggested that disease and immunosuppressants may decrease the ability to supply offspring with protective antibodies, however this was not observed in two observational studies of infants born to mothers with SLE (Motta, 2007; Biggioggero, 2007). Research has shown that women with SLE are at higher risk for infection than women without SLE (Danza, 2013). Furthermore, mouse models have found that high levels of autoantibodies among SLE patients alters fetal development. Neurological effects (dyslexia, autism spectrum disorder) have been identified among children of SLE patients (Vinet, 2015; Neri, 2004). Given that the fetal immune system develops in an immune compromised environment, coupled with the increased maternal risk of infection, it may be postulated that the mothers weakened immunity predisposes a young child to a higher risk of infection.

Only two studies have been identified testing this hypothesis. In a Swedish study of SLE patients and their offspring, SLE during pregnancy was associated with increased infections of infants requiring hospitalization. The focus of the Swedish study was to describe the pregnancy and postpartum experience in SLE and pre-SLE in context with background risks from the general population with infant infection as one outcome. The Swedish study found that 21% of infants born to mothers with SLE during pregnancy had an infection during their first year of life compared with 25% of infants born to mothers pre-SLE diagnosis and 14% of the general population of infants (Arkema, 2016). While a specific mechanism was not discussed, the increased frequency of pre-SLE diagnosis caused the authors to suggest that infant infection may be associated with an altered maternal immunological profile that

occurs before clinical symptoms appear (or are clinically able to be accurately diagnosed). A more recent study found an increased risk of infection and sepsis among infants born to women with SLE within the first 30 days of life (Ignacio, 2018). While a specific mechanism was not discussed, the authors concluded that the observation was largely, though not solely, due to preterm birth.

The goal of the current study of UK data was to assess risk of infection and sepsis, a possible sequela of infection, stratified by three immunologically relevant time periods: the neonatal period (0-28 days), 29 days-6 months and > 6 months through 2 years of age. This thesis, which uses data from a national population-based longitudinal database, will support clinical care, prenatal counseling and obstetric decision making.

METHODS

The Clinical Practice Research Datalink (CPRD) is a longitudinal database that is representative of the UK population. Records are available from 1987 and comprise patient files from general practitioners within the region. There is a wealth of information stored in the database including clinical information, diagnosis codes, tests and medications. There are 660 practices that have contributed data on over 12 million lives to CPRD. The main database within CPRD is named CPRD-Gold. It houses all general practitioner information for a patient and utilizes READ codes for data capture. Several additional databases, which are assembled by social or clinically meaningful grouping, may be purchased and linked for analysis.

Identification of mothers with SLE

CPRD-Gold records from 1987 through the July 2018 data cut were utilized for the study. For the current maternal study population, male patients, patients with less than two years of continuous data and those without an up-to-standard/acceptable and eligibility flags were excluded from the population pool. SLE was defined using READ codes: F371000, F396100, H57y400, K01x400, K01x411, Myu7800, N000.00, N000000, N000100, N000200, N000300, N000400, N000600, N000z00 and Nyu4300 (see Appendix 1). The first occurrence of a READ code for SLE was assigned as the SLE index date (i.e. date of diagnosis). Those with a pregnancy subsequent to SLE index date remained among the eligible SLE patient population. Pregnancies were defined per the validated algorithm put forth by Devine et al (Devine, 2009). Briefly, patient records were checked to verify presence of a valid outcome code. Outcome codes were categorized into three categories, (1) stillbirth, (2) pregnancy loss (spontaneous abortion and termination) and (3) live born. Once the first valid outcome was found, records were then de-duplicated using a 210-day cutoff for categories one and three and a 60-day cutoff for category two.

Pregnancy index date was defined as the earliest pregnancy related READ code found within 280 days prior to the outcome date.

Identification of live born infants

All live born babies from mothers with a delivery date after SLE index date were identified and matched to babies of mothers with no history of SLE in a 1:4 ratio by year of birth and maternal age. In addition to using CPRD-Gold, two additional data linkages were requested for this study: the Mother-baby database, as well as Hospital Episode Statistics (HES) inpatient data. The Mother-baby database provides researchers with the ability to link a mother to her child using patient ID codes and provides parental verification of a mother and child. The HES file was then sought out for the linked baby hospitalization information. CPRD-Gold was used to extract the child's general practitioner records.

Identification of live born infants with infections

Infections and sepsis were identified from both CPRD – Gold, which utilizes READ codes, and from the HES inpatient data, which utilizes International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) codes. Specific READ codes for infections and sepsis are found in Appendix 2 and Appendix 3. For HES data, infections were classified using the Healthcare Cost and Utilization Project (HCUP). The HCUP has generated a Clinical Classification Software (CCS) system that has been validated and collapses ICD codes into clinically meaningful categories. Infections were defined using the multilevel CCS categories: bacterial infection; intestinal infection; other infections; including parasitic; respiratory infection; and viral infection. ICD-10 codes were assigned and merged with the CCS categories using the HCUP tutorial. The specific ICD-10 codes found in these categories are available for perusal on the HCUP website (HCUP, 2019). Sepsis was defined as occurrence of any one of the ICD-10 codes found in Appendix 4. Different coding systems between the two databases prevent

consolidation of GOLD and HES data. Thus, we report general practitioner and hospitalization data separately.

For all infants the number of infections and sepsis episodes was calculated cumulatively for the first two years of life. The data was stratified into three time periods: the neonatal period (birth-28 days), 29 days-6 months and >6 months through 2 years. If a patient's date of birth was incomplete in the patient's record, the maternal file was utilized, and date of delivery used as a proxy for date of birth. Information on SLE medication (i.e. hydroxychloroquine (HCQ), corticosteroids, immunosuppressants, heparin and monoclonal antibodies (i.e. anti CD20) use during pregnancy was ascertained from the mother's CPRD-Gold record.

Statistical Analysis

The cumulative number of infection and sepsis events, i.e. the crude incidence risk ratios, were calculated for infants born to mothers with SLE and infants born to mothers without SLE. Incidence risk ratios were assessed for the entire time period of 0-2 years of life, as well as the three previously described time periods. Intrauterine infection is associated with at least 40% of preterm births, although whether it is a cause of consequence is often difficult to delineate (Agarwal, 2012; Lamont, 2003). In order to remove any impact of collider bias, results were also reported stratified for preterm birth (PTB) (defined and categorized as any birth occurring before gestational week 37) in addition to adjustment for PTB (VanderWeele, 2012). Those with missing gestational age data (thus, PTB not able to be calculated) were removed from all models before analysis. Incidence risk ratios and 95% confidence intervals were calculated based on a modified Poisson regression. This modified Poisson regression is applied to correct variance overestimation that occurs when the classic Poisson regression and allows for the direct estimate of the relative risk estimate (Zou, 2004). Generalized estimating equation (GEE) method was used for the estimation and inference in order to account for correlation

due to duplicate maternal patient IDs (i.e. mothers contributing more than one infant to the study population). These analysis procedures were conducted using similar methodology for both GOLD and HES tables. All statistical analysis was done in SAS Enterprise Guide V 6.1.

RESULTS

General Practitioner Data – CPRD Gold

Six-hundred and thirty-three infants were born to women with SLE and 2,532 infants were born to women without SLE (Table 2.1). Approximately half of the infants (n=3,165) were female in each cohort and the majority of babies were born full-term (Table 2.1). Infants born to mothers with SLE (n=633) were more likely to be born preterm (n=135) compared to those 336 infants not born to an SLE mother (n= 2,532) ($p< 0.05$). The mean average age of the mothers at childbirth was 32 and 29 years for women with SLE and women without SLE, respectively, with the median birth weight nearly identical for the infants born to women with SLE and infants born to women without SLE (2820 g and 2837 g), respectively.

During the first two years of life, 135 and 392 infection events were seen among the 633 infants born to women with SLE and among the 2,532 infants born to women without SLE, respectively (Table 2.2). Thirteen and 17 sepsis events were seen among infants born to women with SLE and infants born to women without SLE, respectively. An 11% increased risk of infection was observed for infants born to women with SLE compared to infants born to women without SLE (RR = 1.11; 95% CI: 1.00-1.44). The effect increased when adjusted (aRR) for preterm birth and maternal age (aRR = 1.25; 95%CI: 0.94, 1.62). When stratified by specific infection categories, those born to mothers with SLE were at increased risk of "other bacterial diseases" (aRR = 3.29; 95%CI: 1.00, 10.86; $p<0.05$) "other urinary system diseases" (aRR = 2.29; 95%CI: 1.00, 5.34; $p<0.05$) even after adjustment for preterm birth. Those

born to women with SLE showed no increased risk of sepsis when compared to infants born to women without SLE.

The study had insufficient power to examine results by time period. Table 2.3 shows "insufficient data" for data where there were less than 16 events. Event counts are available in Appendix 5.

Table 2.4 displays the risk of infection for those with SLE when stratified by preterm birth. Compared those infants born to mothers without SLE, those born prematurely has an increased risk of infection between 29 days and 6 months (RR = 3.56; 95%CI: 1.35, 9.34; $p<0.05$).

Hospitalization data – HES

Two hundred seventy-one (271) infants born to mothers with SLE and 1,083 infants born to women without SLE were gathered for hospitalization data (Table 2.5). Approximately half of the infants were female in each cohort and the majority of babies were born full-term. Infants born to mothers with SLE were more likely to be born preterm compared to those not born to a mother with SLE ($p< 0.05$). The mean average age of the mothers at childbirth was 32 and 30 years, respectively, for mothers with SLE and for mothers without SLE. A similar median birth weight was observed for the those born to women with SLE and those born to women without SLE (3015 g; 3172 g, respectively).

During the first two years of life, 50 and 184 infection events were seen among 41 SLE infants born to women without SLE and 1,083 infants born to women without SLE, respectively (Table 2.6). Ten and 47 sepsis events were seen among those born to women with SLE and those without SLE, respectively. The most common infection code causing hospitalization was "viral infection, unspecified". No additional risk of infection was observed among the infants born to mothers with SLE compared to infants born to women without SLE. While a slightly lower risk of sepsis was observed among infants born to women without SLE (RR = 0.85, 95%CI: 0.43, 1.68) the results were not statistically significant,

thus no firm observations can be made. Table 2.7 shows the risk of infection stratified by age category. While the risk of infection may be higher among infants born to women with SLE compared to women without SLE (RR =1.46), additional studies would need to be conducted to verify this finding as the result did not reach statistical significance.

DISCUSSION

While the risk of infection during pregnancy has been shown to be increased among women with SLE, few studies have investigated the infection and the subcategory of sepsis risk among offspring of mothers with SLE.

The current thesis investigates both sepsis and infection risk in those born to mothers with SLE during the first two years of life stratified by time period. The vast scope of CPRD was leveraged to investigate these outcomes both in a general practitioner setting in addition to the hospitalization setting. Previous publications have restricted analysis to the hospital setting. Unlike the previous studies, this thesis addressed the 2-year infection and sepsis risks in the general practitioner database. Additionally, this thesis analyzed three stratified time periods, the neonatal period, the post-neonatal period (29 days – 6 months) and 6+ months through two years in two healthcare settings (i.e. general practitioner and hospital). Because many infections in infants are not severe enough to warrant hospitalization, it was anticipated that data from CPRD-Gold would have a larger sample size and thus outcome events for analysis; this was observed in the data.

Results of this thesis show a slight association between SLE and 2-year infection rates before and after adjusting for preterm birth and maternal age. This association, however, is not statistically significant (aRR = 1.24; 95%CI: 0.94, 1.62). When stratifying by specific infection categories, outcomes showed an increased risk in some categories. Specifically, an increased risk of "other urinary tract infections" (aRR = 2.29; 95%CI: 1.00, 5.25) and "other bacterial infections" (aRR = 3.29; 95%CI: 1.00, 10.86) was observed after adjustment for preterm birth and maternal age. It is unclear why these specific infection types are associated with SLE; however, one possibility may be maternal microchimerism. Microchimerism, described as maternal cells in the fetal circulation, occurs in 42% of normal pregnancies and can last for years after birth (Lo, 1996; Artlet, 2000; Stevens, 2003). Maternal microchimerism has been identified in patients with SLE and has been associated with neonatal lupus,

dyslexia and reduced tetanus vaccine efficacy. (Stevens, 2003; Wolen, 1984; Motta, 2008). Urinary tract infections are usually associated with bacterial infections and a study of infections among SLE patients show high prevalence of urinary tract infections (UTI) (Hidalgo-Tenorio, 2004; Danza 2013). While further studies are warranted, I am speculating that maternal microchimerism may be associated with UTI, explaining the increased risk of these specific infection types (as opposed to the other infection categories) among the infants born to mothers with SLE.

Two studies have been published in the literature addressing infection risk in the offspring of women with SLE. A recent study observing the risk of perinatal infection among women with SLE and their infants found a crude increased risk for infection (RR = 1.8; 95% CI: 1.3, 2.6) and sepsis (RR = 1.2; 95% CI: 0.7, 2.0) during the neonatal period (Ignacio, 2018). However, when adjusted for maternal age and gestational age, the risk did not reach statistical significance for either outcome. The current thesis had insufficient power to examine the impact of time i.e. neonatal and infant lifetime periods. Thus, this thesis was not able to verify the neonatal period findings reported by Ignacio et al.

Arkema et al., published in 2016, suggests an increased risk of infection among offspring born to women with SLE. The study investigated the first 5 years of life and found that 21% of infants born to mothers with SLE had a serious infection requiring hospitalization during the first year of life compared to 14% in the general population (Arkema, 2016). Data from this thesis did not show an increased risk of hospitalization due to infection and sepsis; however, sample size was more limited for this population.

Strengths and Limitations

This is the first known paper to report the risk of SLE and 2-year infection/sepsis among offspring of women with SLE. It is also the first known paper to address infections outside of the hospital setting (i.e. general practitioner database). With respect to data capture of SLE, data were sought since the inception of the database (i.e. 1987) thus, all SLE patients meeting inclusion criteria were captured in

this study. SLE patients in this study showed an extremely low frequency of medication use during pregnancy (<1%; data not shown) thus medication use was not available for analysis. This may suggest that our population of SLE patients had been selected for a milder course of disease based on our exclusion criteria. While immunosuppressants cross the placental barrier and may impact development of the infant immune system interfering with both humoral and cellular immunity, (Flechner, 1985; Venkataranman, 1998, Cote, 1974; DeWitte, 1984; Davison, 1985) no decrease in immune function has been reported in infants born to women with SLE (Motta, 2007; Biggioggero, 2007).

Preterm birth in the UK is nationally around 7% of all births, with Blacks having a higher frequency than the non-whites population (Blencowe, 2012; Tommy's.org, 2018). Non-whites also have a higher prevalence of SLE (Hiraki, 2012). Results within the general practitioner database show a higher frequency of preterm birth among infants born to women without SLE (13%) compared to the national average of 7%. Known risk factors of preterm birth include previous preterm birth, urinary tract infections, diabetes and being non-white and hypertension (Andrews, 2000). Adjustment was made for preterm birth to account for this noted difference seen between the two study cohorts. Stratification by preterm birth type (i.e. iatrogenic, premature rupture of membranes and spontaneous) was not available for analysis. This thesis was also unable to assess any protective effects of breastfeeding on infection due to that large frequency (>80%) of missing data in the database.

Conclusions

Infants to mothers with SLE do not appear to be at increased risk of infection overall but may be at a small increased risk of UTI and other bacterial infections. Further research is needed to clarify these associations.

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TABLES AND FIGURES

Table 2.1: Baseline Characteristics of Live Infants linked via Mother Baby Linkage with Eligible General Practitioner Database (CPRD-Gold)

		Infants born to Women with SLE	Infants born to Women without SLE	
Characteristics		**N (%)**	**N (%)**	**p-value**
N		633	2,532	
Gender	Female	310 (49.0%)	1,240 (49.0%)	1.00
	Male	323 (51.0%)	1,292 (51.0%)	
Gestational age at birth (wks)	Missing	107 (16.9%)	484 (19.1%)	<0.0001
	24-30+6	40 (6.3%)	77 (3.0%)	
	31-36+6	95 (15.0%)	259 (10.2%)	
	37-40+6	339 (53.7%)	1,191 (47.0%)	
	40+	52 (8.2%)	521 (20.6%)	
Maternal age at birth (yrs)	N	633	2532	<0.001
	Mean (SD)	32.3 (SD=5.5)	29.8 (SD=5.8)	
	Min, Max	17, 46	15, 47	
Birth weight (g)	N	315	1204	0.52
	Median	2820.0	2837.5	

Table 2.2: Risk of Infections and Sepsis during the first two years of life among Infants born to women with SLE (n=633) compared to Infants Born to Women without SLE (n=2,532) found in the General Practitioner Database (CPRD-Gold)

Infection Group	Maternal Status of Infant	Number of Infection Events	Percentage of Infants	Risk Ratio	95% Confidence Interval
ALL INFECTIONS	SLE	135	15.0	1.11[†] 1.24[‡]	(1.00, 1.44) (0.94, 1.62)
	without SLE	392	12.3	---	---
Acute respiratory infections	SLE	63	6.8	1.06	(0.70, 1.50)
	without SLE	189	5.8	---	---
Arthropathies and related disorders	SLE	4	0.2	---	---
	without SLE	0	0.0	---	---
Diseases of the ear and mastoid process	SLE	11	1.3	2.44	(1.15, 5.18)
	without SLE	18	0.5	---	---
Disorders of eye and adnexa	SLE	4	0.6	1.60	(0.50, 5.10)
	without SLE	10	0.4	---	---
Intestinal infectious diseases	SLE	19	2.4	0.84	(0.52, 1.39)
	without SLE	90	3.2	---	---
Mycoses	SLE	2	0.3	1.00	(0.21, 4.71)
	without SLE	8	0.3	---	---
Oral cavity, salivary glands and jaw diseases	SLE	0	0.0	---	---
	without SLE	1	0.0	---	---
Other bacterial diseases	SLE	5	0.8	3.24[†] 3.29[‡]	(1.02, 10.62) (1.00, 10.86)
	without SLE	6	0.2	---	---
Other perinatal conditions	SLE	5	0.8	1.18	(0.43, 3.19)
	without SLE	17	0.7	---	---
Other specified perinatal conditions	SLE	0	0.0	---	---
	without SLE	1	0.0	---	---
Other urinary system diseases	SLE	15	1.7	1.76 2.29[†‡]	(0.85, 3.74) (1.00, 5.25)
	without SLE	34	1.2	---	---
Other viral and chlamydial diseases	SLE	0	0.0	---	---
	without SLE	1	0.0	---	---
Skin and subcutaneous tissue infections	SLE	5	0.8	1.42	(0.52, 3.97)
	without SLE	14	0.6	---	---
Surgical and medical care complications NEC	SLE	2	0.3	2.67	(0.44, 15.96)
	without SLE	3	0.1	---	---
SEPSIS	SLE	13	1.6	1.83[†]	(0.84, 4.22)
	without SLE	17	0.7	---	---

Infection Group	Maternal Status of Infant	Number of Infection Events	Percentage of Infants	Risk Ratio	95% Confidence Interval

NEC = not elsewhere classified; † = $p<0.05$; ‡ = adjusted for maternal age and preterm birth

Table 2.3: Risk of Infections and Sepsis among infants born to women with SLE compared to infants born to women without SLE stratified by age range in the General Practitioner Database (CPRD – Gold)

	Neonatal Period			29 days – 6 months			>6 months to 2 years		
Infection Group	Number of Infection Events†	Risk Ratio	95% confidence interval	Number of Infection Events†	Risk Ratio	95% confidence interval	Number of Infection Events†	Risk Ratio	95% confidence interval
ALL INFECTIONS	**9**	**1.38**	**(0.65, 2.95)**	**26**	**1.58†** **0.99‡†**	**(1.00, 2.48)** **(0.97, 1.00)**	**100**	**1.10†**	**(0.80, 1.47)**
Acute Respiratory Infections	---	ISD	---	8	ISD	---	55	1.14†	(0.80, 1.52)
Arthropathies and related disorders	---	ISD	---	4	ISD	---	---	ISD	---
Diseases of the ear and mastoid process	---	ISD	---	---	ISD	---	11	2.93† 1.74‡†	(1.35, 6.39) (0.45, 6.64)
Disorders of eye and adnexa	---	ISD	---	3	ISD	---	1	ISD	---
Intestinal infectious diseases	---	ISD	---	3	ISD	---	16	0.81	(0.47, 1.39)
Mycoses	1	ISD	---	1	ISD	---	---	ISD	---
Oral cavity, salivary glands and jaw diseases	---	ISD	---	---	ISD	---	---	ISD	---
Other bacterial diseases	3	ISD	---	1	ISD	---	1	ISD	---
Other perinatal conditions	3	ISD	---	2	ISD	---	---	ISD	---
Other specified perinatal conditions	---	ISD	---	1	ISD	---	---	ISD	---
Other urinary system diseases	2	ISD	---	3	ISD	---	10	1.60 2.05‡	(0.77, 3.33) (0.75, 5.60)
Other viral and chlamydial diseases	---	ISD	---	---	ISD	---	---	ISD	---
Skin and subcutaneous tissue infections	---	ISD	---	1	ISD	---	4	ISD	---
Surgical and medical care complications NEC	---	ISD	---	---	ISD	---	2	ISD	---
SEPSIS	**3**	ISD	---	**6**	ISD	---	**4**	ISD	---

NEC = not elsewhere classifiable; † $p < 0.05$; ‡ = adjusted for preterm birth and maternal age; ISD = insufficient data; † = among infants born to women with SLE

Table 2.4: Relative Risk (RR) of All Infections Stratified by Preterm Birth, Shown by Time Period

	Preterm		Full term	
Time Period	**RR**	**95% Confidence Interval**	**RR**	**95% Confidence Interval**
0-2 years	1.51	(0.86, 2.66)	1.89†	(1.03, 3.45)
Neonatal Period	0.99	(0.19, 5.13)	1.21	(0.45, 3.28)
Post neonatal period	3.56†	(1.35, 9.34)	1.09	(0.53, 2.25)
6+ months – 2 years	1.27	(0.63, 2.55)	1.17	(0.82, 1.66)

† = $p < 0.05$

Table 2.5: Demographics of Live Infants linked via Mother Baby Linkage with Eligible HES Data

		Infants born to Women with SLE	Infants born to Women without SLE	
Characteristics		**N (%)**	**N (%)**	**p-value**
N	N	271	1,083	
Gender	Female	133 (49.1%)	531 (49.0%)	0.99
	Male	138 (50.9%)	552 (51.0%)	
Gestational age at birth (wks)	Missing	19 (7.0%)	74 (6.8%)	<0.001
	24-30+6	10 (3.7%)	40 (3.7%)	
	31-36+6	43 (15.9%)	93 (8.6%)	
	37-40+6	175 (64.6%)	608 (56.1%)	
	> 40+6	24 (8.9%)	268 (24.7%)	
Maternal age at birth (yr)	N	271	1083	<0.001
	Mean (SD)	32.3 (SD=5.8)	30.1 (SD=5.9)	
	Min, Max	19, 46	15, 48	
Birth weight (g)	N	191	779	<0.001
	Median	3015.0	3172.0	
	Min, Max	2, 4680	2, 5166	

Table 2.6: Risk of Infections and Sepsis During the First Two Years of Life Among Infants Born to Women with SLE (N=271) Compared to Infants Born To Women Without SLE (n=1083)

Infection Group	Maternal Status of Infant	Number of Infection Events	Risk Ratio	95% confidence interval
ALL INFECTIONS	SLE	50	1.09	(0.79, 1.48)
	without SLE	184		
Bacterial infection	SLE	19	1.08	(0.65, 1.80)
	without SLE	70		
Intestinal infection	SLE	9	1.38	(0.65, 2.95)
	without SLE	26		
Other infections; including parasitic	SLE	0	---	---
	without SLE	3		
Viral infection	SLE	22	0.91	(0.58, 1.46)
	without SLE	96		
SEPSIS	SLE	10	0.85	(0.43, 1.68)
	without SLE	47		

Table 2.7: Risk of Infections and Sepsis among infants born to women with SLE compared to infants born to women without SLE stratified by age range

	Neonatal Period			29 days – 6 months			>6 months - 2 years		
Infection Group	**Number of Infection Events†**	**Risk Ratio**	**95% confidence Interval**	**Number of Infection Events†**	**Risk Ratio**	**95% confidence Interval**	**Number of Infection Events†**	**Risk Ratio**	**95% confidence Interval**
ALL INFECTIONS	**15**	**1.46**	**(0.81, 2.64)**	**10**	**1.11**	**(0.55, 2.23)**	**25**	**0.93**	**(0.60, 1.44)**
Bacterial infection	13	1.37	(0.73, 2.57)	3	0.71	(0.21, 2.41)	3	0.80	(0.23, 2.76)
Intestinal infection	0	---	---	1	0.67	(0.08, 5.53)	8	1.60	(0.70, 3.63)
Other infections; including parasitic	0	---	---	0	---	---	0	---	---
Viral infection	2	2.00	(0.37, 10.91)	6	1.84	(0.70, 4.85)	14	0.71	(0.40, 1.25)
SEPSIS	**7**	**0.90**	**(0.40, 2.05)**	**2**	**0.57**	**(0.13, 2.51)**	**1**	**2.00**	**(0.18, 22.04)**

†=Among infants born to women with SLE

CONCLUSION

The purpose of this thesis was to investigate obstetric outcomes of women with SLE and whether there was an increased risk of infection episodes for the offspring. Data from this research can be used to assist with family planning and inform clinical care for women with SLE. A trend showing increased frequencies of outcomes was seen among the SLE population. Specifically, the frequency of caesarian section (25.8% vs. 22.5%), preterm birth (9.2% vs. 6.2%), miscarriage (18.7% vs. 16.8%), and stillbirth (0.7% vs. 0.4%) was higher among women with SLE. While most outcomes showed an approximate 15% increase in frequency compared to women without SLE, preterm birth and stillbirth showed over a 45% increase in frequency.

The first study found that outcomes of interest: placental abruption; caesarian section (emergency and elective); miscarriage (fetal loss <24 weeks gestation); elective termination; preterm birth (live born <37 weeks gestation) and stillbirth (fetal death and expulsion 24+ weeks gestation) were seen in higher frequency compared to women without SLE. Women with SLE have approximately 44% higher risk of caesarian section than women without SLE ($p<0.05$). Because of the large amount of missing data for the variable race, this covariate was not able to be assessed. Nor was the impact of medication use during pregnancy assessed, as our study population had less than 1% use during this time period.

The second study assessed the susceptibility of infection and sepsis for live born infants aged 0-2 years, born to women with SLE and compared this risk of infection to infants born to women without SLE. The study also stratified infection and sepsis risk by three time periods (0-28 days, 29 days – 6 months, and >6 months).

Infants to mothers with SLE do not appear to be at increased risk of infection overall but may be at a small increased risk of UTI and other bacterial infections. Further research is needed to clarify these associations. Low frequencies of organ involvement and medication use suggest that this

thesis may have comprised of an SLE cohort with milder disease. Patients with SLE are recommended to be flare-free for 6 months before family planning and thus; results from this thesis may be generalizable to a vast majority of women with SLE. It may be reassuring to the SLE patient with mild disease and their treating physician to have evidence that a successful pregnancy is probable.

APPENDICIES

APPENDIX 1

SYSTEMIC LUPUS ERYTHEMATOSUS READ CODE LIST[1]

READ Code	Description
F371000	Polyneuropathy in disseminated lupus erythematosus
F396100	Myopathy due to disseminated lupus
H57y400	Lung disease with systemic lupus erythematosus
K01x400	Nephrotic syndrome in systemic lupus erythematosus
K01x411	Lupus nephritis
Myu7800	[X]Other local systemic lupus erythematosus
N000.00	Systemic lupus erythematosus
N000000	Disseminated lupus erythematosus
N000100	Libman-Sacks disease
N000300	Systemic lupus erythematosus with organ or system involvement
N000400	Systemic lupus erythematosus with pericarditis
N000600	Cerebral lupus
N000z00	Systemic lupus erythematosus NOS
Nyu4300	[X]Other forms of systemic lupus erythematosus

APPENDIX 2

INFECTION READ CODE LIST[1]

Subchapter/ READ code	Description
A....00	Infectious and parasitic diseases
H0...00	Acute respiratory infections
H2...00	Pneumonia and influenza
M0...00	Skin and subcutaneous tissue infections
1789	Asthma trigger - respiratory infection
2Fd0.00	Eron class I skin and soft tissue infection
2Fd2.11	Eron class 3 skin and soft tissue infection
2J23.00	Hepatitis A - current infection
65R..00	Isolation because of infection
8HBQ000	Sexually transmitted infection in-house follow-up
C37y900	Haemophagocytic syndrome, infection-associated
D201200	Aplastic anaemia due to infection
D201211	Hypoplastic anaemia due to infection
D400400	Agranulocytosis due to infection
D400411	Neutropenia due to infection
F033.00	Encephalitis due to other infection EC
F033z00	Unspecified encephalitis due to other infection EC
F400500	Eye infection
F4C0.11	Eye infection
F4Cy000	Filarial infection of conjunctiva
F501200	Acute infection of pinna
F501900	Other acute external ear infections
F52z.11	Infection ear
Gy4..00	Infection of dialysis vascular access
Gy40.00	Infection of dialysis arteriovenous graft
Gy41.00	Infection of dialysis arteriovenous fistula
J024.11	Dental infection
J065.11	Infection of tooth socket
J083z11	Infection mouth
J574G00	Perianal infection
K10..00	Infections of kidney
K10..11	Renal infections
K10z.00	Infection of kidney NOS
K180000	Urethral stricture due to unspecified infection
K180100	Urethral stricture due to infection EC
K190.00	Urinary tract infection, site not specified
K190.11	Recurrent urinary tract infection

K190200	Post operative urinary tract infection
K190300	Recurrent urinary tract infection
K190400	Chronic urinary tract infection
K190500	Urinary tract infection
K190z00	Urinary tract infection, site not specified NOS
K272.11	Infection of penis
K310800	Breast infection
K40z.12	Female pelvic infection
N12zG00	Infection of intervertebral disc - pyogenic
N22yC00	Pyogenic infection of tendon sheath
N23y600	Palmar space infection, thenar
N23y700	Palmar space infection, mid-palm
N23y800	Palmar space infection, hypo-thenar
N30..00	Osteomyelitis, periostitis, other infections affecting bone
N300.12	Acute bone infection
N302.11	Bone infection
N302A00	Infection of cervical spine
N302B00	Infection of thoracic spine
N302C00	Infection of lumbar spine
N302D00	Infection of sacrum
N302E00	Infection of coccyx
N302F00	Infection of clavicle
N302G00	Infection of scapula
N302H00	Infection of humerus
N302K00	Infection of ulna
N302M00	Infection of metacarpal
N302N00	Infection of phalanx of finger or thumb
N302P00	Infection of pelvis
N302Q00	Infection of femur
N302R00	Infection of patella
N302S00	Infection of tibia
N302T00	Infection of fibula
N302U00	Infection of calcaneum
N302V00	Infection of talus
N302W00	Infection of other tarsal bone
N302X00	Infection of metatarsal
N302Y00	Infection of phalanx of toe
N30y.00	Other infections involving bone
N30y400	Other infections involving bone, of the hand
N30y500	Other infections involving bone, of the pelvic region/thigh
N30y600	Other infections involving bone, of the lower leg
N30y700	Other infections involving bone, of the ankle and foot
N30yz00	Other infections involving bone, NOS

N30z.00	Bone infection NOS
N30z000	Bone infection NOS, of unspecified site
N30z200	Bone infection NOS, of the upper arm
N30z400	Bone infection NOS, of the hand
N30z500	Bone infection NOS, of the pelvic/thigh
N30z600	Bone infection NOS, of the lower leg
N30z700	Bone infection NOS, of ankle and foot
N30z800	Bone infection NOS, of other specified site
N30z900	Bone infection NOS, of multiple sites
N30zz00	Bone infection NOS
Q40..00	Infections specific to perinatal period
Q401.00	Congenital cytomegalovirus infection
Q402.00	Other congenital infections
Q402z00	Other congenital infection NOS
Q404.11	Umbilical stump infection of the newborn
Q407.00	Neonatal candida infection
Q407y00	Other specified neonatal candida infection
Q407z00	Neonatal candida infection NOS
Q408.00	Intra-amniotic fetal infection
Q408200	Eschericha coli intra-amniotic fetal infection
Q408600	Pseudomonas pyocyaneus congenital infection
Q408z00	Intra-amniotic fetal infection NOS
Q409000	Congenital hepatitis A infection
Q409100	Congenital hepatitis B infection
Q40y.00	Other specified perinatal infection
Q40y100	Neonatal urinary tract infection
Q40yz00	Other specified perinatal infection NOS
Q40z.00	Perinatal infections NOS
Q431200	Perinatal jaundice from infection
Q47y200	Neonatal skin infection
SD0zz00	Superficial injury of head NOS, infection NOS
SD1zz00	Superficial injury of trunk NOS, infection NOS
SD2zz00	Superficial injury shoulder/upper arm, infection NOS
SK03.00	Post-traumatic wound infection NEC
SP05611	[X]Graft infection
SP05612	[X]Prosthetic infection
SP06.00	Infection and inflammation due to internal prosthetic device
SP06.12	Infection due to internal prosthetic device,implant or graft
SP06500	Infection of bone graft
SP06600	Infection of bone allograft
SP06700	Infection of internal Kirschner wire fixator
SP06800	Infection and inflamm reac due inter ortho device
SP06A00	Infection of totally implantable venous access device

SP06A11	Infection of implantable venous access port
SP06C00	Infection associated with intrauterine contraceptive device
SP06E00	Infection and inflammation associated with retained IUCD
SP07Q00	Catheter-associated urinary tract infection
SP07Q11	CAUTI - catheter-associated urinary tract infection
SP0D000	Infection associated with artificial insemination
SP13200	Post operative chest infection
SP16200	Chronic infection of amputation stump
SP25.00	Postoperative infection
SP25500	Postoperative wound infection, unspecified
SP25600	Postoperative wound infection-deep
SP25700	Postoperative wound infection-superficial
SP25800	MRSA infection of postoperative wound
SP25z00	Postoperative infection NOS
SP33.00	Infection after injection/infusion/transfusion/vaccination
SP33000	Infection after infusion
SP33100	Infection after injection
SP33200	Infection after transfusion
SP33300	Infection after vaccination
SP33400	Infection following immunization
SP33500	Infection of intravenous catheter
SP33z00	Infection after injection/infusion/transfusion/vacc NOS
SyuJ000	[X]Post-traumatic wound infection, not elsewhere classified
SyuK511	[X] Vascular graft infection
Z262J11	Placental infection
ZA13A00	Drainage of nail fold infection

APPENDIX 3

SEPSIS READ CODE LIST[1]

Qyu4200	[X]Other bacterial sepsis of newborn
Q40A100	Sepsis of newborn due to Escherichia coli
Q40y011	Congenital sepsis NOS
A3C0300	Sepsis due to Streptococcus pneumoniae
A396.00	Sepsis due to Actinomyces
K190600	Urosepsis
Qyu4100	[X]Sepsis/newborn due to other+unspecified staphylococcus
H5y0100	Tracheostomy sepsis
A3C1z00	Sepsis due to staphylococcus NOS
A3Cz.00	Sepsis NOS
L40..11	Sepsis - puerperal
A3C3.11	Sepsis due to Gram negative organisms
Q40W.00	Sepsis of newborn due to other+unspecified streptococci
J666.00	Biliary sepsis
Qyu4800	[X]Sepsis of newborn due to other+unspecified streptococci
A3C0.00	Sepsis due to Streptococcus
A3C0z00	Streptococcal sepsis, unspecified
A3C1000	Sepsis due to Staphylococcus aureus
A3C1y00	Sepsis due to other specified staphylococcus
A3C2.11	Sepsis due to anaerobes
A3C3.00	Sepsis due to Gram negative bacteria
A3C1.00	Sepsis due to Staphylococcus
A3C0y00	Other streptococcal sepsis
A3C0100	Sepsis due to Streptococcus group B
A3C2.00	Sepsis due to anaerobic bacteria
Q40A.00	Sepsis of the newborn
A3C..00	Sepsis
A270611	Listerial sepsis
AB2y511	Sepsis due to Candida
A3Cy.00	Other specified sepsis
A3C3y00	Sepsis due to other Gram negative organisms
A38z.11	Sepsis
A3C0000	Sepsis due to Streptococcus group A
A270600	Sepsis due to Listeria monocytogenes
A023.00	Salmonella sepsis
Q40A200	Sepsis of newborn due to anaerobes
Q40A000	Sepsis of newborn due to Staphylococcus aureus
A365.00	Meningococcal meningitis with acute meningococcal septicaem
A380300	Septicaemia due to streptococcus pneumoniae
A38y.00	Other specified septicaemias

A366.00	Meningococcal meningitis with meningococcal septicaemia
G52y300	Septic myocarditis - pneumococcal
Q407511	Neonatal monilial septicaemia
Ayu3E00	[X]Other streptococcal septicaemia
A384100	Haemophilus influenzae septicaemia
A98yz12	Gonococcal septicaemia
A202.00	Septicaemic plague
L293.00	Septicaemia during labour
A380400	Septicaemia due to enterococcus
R055500	[D]Septic shock
A272100	Pasteurella septic infection (cat or dog bite)
L433.12	Septic obstetric embolism
L090z00	Septicaemia NOS following abortive pregnancy
A384211	E.coli septicaemia
A270100	Listeria septicaemia
A380500	Vancomycin resistant enterococcal septicaemia
A271100	Erysipelothrix septicaemia
A380000	Septicaemia due to streptococcus, group A
A383.00	Septicaemia due to anaerobes
A384400	Serratia septicaemia
G52y400	Septic myocarditis - staphylococcal
Q40y200	Septicaemia of newborn
L403100	Puerperal septicaemia - delivered with postnatal comp
A381.00	Staphylococcal septicaemia
R055511	[D]Septicaemic shock
SP25400	Postoperative septicaemia
A384200	Escherichia coli septicaemia
A380100	Septicaemia due to streptococcus, group B
Q40y012	Congenital septicaemia
L293100	Septicaemia during labour - delivered
L403000	Puerperal septicaemia unspecified
A382.00	Pneumococcal septicaemia
A380.00	Streptococcal septicaemia
A384.00	Septicaemia due to other gram negative organisms
A381100	Septicaemia due to coagulase-negative staphylococcus
G52y600	Septic myocarditis NOS
SP38000	Septic shock due to transfusion
Ayu3J00	[X]Septicaemia, unspecified
A384300	Pseudomonas septicaemia
M07z.13	Septic spots
A362.00	Meningococcal septicaemia
M080.12	[X]Septic thumb
J67y300	Aseptic necrosis of pancreas

L403.00	Puerperal septicaemia
Q407500	Neonatal candida septicaemia
A384z00	Other gram negative septicaemia NOS
A021.00	Salmonella septicaemia
Ayu3G00	[X]Septicaemia due to other gram-negative organisms
A545.00	Herpes simplex septicaemia
AB2y300	Candidal septicaemia
SP20100	Postoperative septic shock
A381000	Septicaemia due to Staphylococcus aureus
Ayu3F00	[X]Streptococcal septicaemia, unspecified
Ayu3H00	[X]Other specified septicaemia
L096600	Septic embolism following abortive pregnancy
N010.11	Septic arthritis
A384000	Gram negative septicaemia NOS
A38..00	Septicaemia
A38z.00	Septicaemia NOS

APPENDIX 4

SEPSIS ICD-10 CODE LIST[1]

ICD-10 Code	Description
A40.0	Sepsis due to streptococcus, group A
A40.1	Sepsis due to streptococcus, group B
A40.8	Other streptococcal sepsis
A40.9	Streptococcal sepsis, unspecified
A41.2	Sepsis due to unspecified staphylococcus
A41.0	Sepsis due to Staphylococcus aureus
A41.0Z16	Sepsis due to Staphylococcus aureus Infection with drug resistant microorganisms
A41.1	Sepsis due to other specified staphylococcus
A40.3	Sepsis due to Streptococcus pneumoniae
A41.4	Sepsis due to anaerobes
A41.50	Gram-negative sepsis, unspecified
A41.3	Sepsis due to Hemophilus influenza
A41.51	Sepsis due to Escherichia coli
A41.52	Sepsis due to pseudomonas
A41.53	Sepsis due to serratia
A41.59	Other gram-negative sepsis
A41.81	Sepsis due to Enterococcus
A41.89	Other specified sepsis
A41.9	Sepsis, unspecified
R65.20	Severe sepsis without septic shock
R65.21	Severe sepsis with septic shock
R65.10	SIRS of non-infectious origin without acute organ dysfunction
R65.11	SIRS of non-infectious origin with acute organ dysfunction
P36.0	Sepsis of newborn due to streptococcus, group B
P36.10	Sepsis of newborn due to unspecified streptococci
P36.19	Sepsis of newborn due to other streptococci
P36.2	Sepsis of newborn due to staphylococcus aureus
P36.30	Sepsis of newborn due to unspecified staphylococci
P36.39	Sepsis of newborn due to other staphylococci
P36.4	Sepsis of newborn due to Escherichia coli
P36.5	Sepsis of newborn due to anaerobes
P36.8	Other bacterial sepsis of newborn
P36.9	Bacterial sepsis of newborn, unspecified

APPENDIX 5

	Neonatal Period			29 days – 6 months			>6 months to 2 years		
Infection Group	**Number of Infection Events[†]**	**Risk Ratio**	**95% confidence interval**	**Number of Infection Events[†]**	**Risk Ratio**	**95% confidence interval**	**Number of Infection Events [†]**	**Risk Ratio**	**95% confidence interval**
ALL INFECTIONS	**9**	**1.38**	**(0.65, 2.95)**	**26**	**1.58[†]** **0.99[‡†]**	**(1.00, 2.48)** **(0.97, 1.00)**	**100**	**1.10[†]**	**(0.80, 1.47)**
Acute Respiratory Infections	0	---	---	8	1.00	(0.46, 2.17)	55	1.14[†]	(0.80, 1.52)
Arthropathies and related disorders	---	---	---	4	---	---	---	---	---
Diseases of the ear and mastoid process	---	---	---	0	---	---	11	2.93[†] 1.74[‡†]	(1.35, 6.39) (0.45, 6.64)
Disorders of eye and adnexa	---	---	---	3	3.00	(0.67, 13.40)	1	0.67	(0.08, 5.54)
Intestinal infectious diseases	0	---	---	3	1.20	(0.33, 4.37)	16	0.81	(0.47, 1.39)
Mycoses	1	---	---	1	1.00	(0.11, 8.95)	0	---	---
Oral cavity, salivary glands and jaw diseases	---	---	---	---	---	---	0	---	---
Other bacterial diseases	3	2.00 2.04[‡]	(0.50, 8.00) (0.50, 8.37)	1	---	---	1	---	---
Other perinatal conditions	3	0.86[u]	(0.25, 2.98)	2	2.67	(0.44, 15.96)	---	---	---
Other specified perinatal conditions	0	---	---	1	1.00	(0.1, 8.95)	---	---	---
Other urinary system diseases	2	4.00[u]	(0.56, 28.39)	3	1.71	(0.43, 6.63)	10	1.60 2.05[‡]	(0.77, 3.33) (0.75, 5.60)
Other viral and chlamydial diseases	---	---	---	---	---	---	0	---	---
Skin and subcutaneous tissue infections	0	---	---	1	4.00	(0.25, 63.95)	4	1.33 0.71[‡]	(0.43, 4.13) (0.15, 3.26)
Surgical and medical care complications NEC	---	---	---	0	---	---	2	8.00	(0.73, 88.23)

	Neonatal Period			29 days – 6 months			>6 months to 2 years		
Infection Group	**Number of Infection Events†**	**Risk Ratio**	**95% confidence interval**	**Number of Infection Events†**	**Risk Ratio**	**95% confidence interval**	**Number of Infection Events †**	**Risk Ratio**	**95% confidence interval**
SEPSIS	**3**	**1.20[u]**	**(0.33, 4.36)**	**6**	**24.00[†]** **8.03[‡]**	**(2.89, 199.34)** **(0.70, 92.20)**	**4**	**2.67**	**(0.75, 9.45)**
† = among infants born to women with SLE									

NEC = not elsewhere classifiable; † $p < 0.05$; ‡ = adjusted for preterm birth and maternal age; u = unable to adjust for preterm birth due to "0" cells

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