PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

The association between maternal systemic lupus erythematosus and infant infection: a population-based cohort study in Sweden

Authors

Gernaat, Sofie A.M.; Simard, Julia; Altman, Maria; Svenungsson, Elisabet; Arkema, Elizabeth

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Barnado, April**
Affiliation	**Vanderbilt University Medical Center**
Date	**12-Sep-2024**
COI	**None**

Gernaat et al. conduct a retrospective cohort study to examine the risk of infection in infants born to SLE mothers compared to infants born to non-SLE mothers and the impact of preterm birth on infection risk. The authors included 1,248 SLE offspring and 34,886 non-SLE offspring from Medical Birth Register. They found higher risk of infection in SLE offspring than non-SLE offspring, particularly in the first 72h after delivery, that was primarily due to preterm birth. They could elaborate on their rationale for using causal mediation analysis and more details on how their control and SLE populations were selected. Overall, this is a relevant and useful topic that I believe many clinicians would be interested in reading.

Major:

1. Can you give rationale why the 72 hours was used?

2. I would explain your rationale for using causal mediation analysis, as this technique may not be familiar, particularly to a clinical audience.

3. You mention that controls were matched in the database. Did you exclude any conditions in controls, such as other autoimmune diseases?

4. I would explain why you excluded SLE mothers with only 1 visit for SLE prior to delivery. Are there concerns this was not an accurate diagnosis? If these were true cases is there another rationale for excluding, i.e new diagnosis, incomplete data/missingness?

5. It would be helpful to give more details to justify why only using 2 or more ICD-10 codes for SLE. A reference is given, but it would be helpful to give the PPV or some performance metric of this phenotyping approach. Further, please clarify why the first SLE discharge code was used as a proxy for diagnosis.

6. Was there any consideration to adjust by gestational age as a continuous variable as opposed to categorical (term, <37 weeks, <32 weeks)?

7. Last part of sentence on page 17 first paragraph- “perhaps being extra careful with hospital discharge in first 72h” seems a little strong and vague. We don’t know, for example, that hours 72-96 have a decreased rate of infection. The data presented here is for <72h, compared to 30d. As you reference, in clinical practice we divide neonatal sepsis into early onset <72h or late onset 72h-7d of life. Similarly, regarding the comment on page 18 about “early discharge”, in the US most term infants are discharged at 48 to 72 hours and early discharge is considered < 48 hours. To your point there are “early-onset sepsis calculators” that can assess risk when considering discharge. It is reasonable to recommend considering SLE as a risk factor when considering early discharge. I would more strongly link your final recommendations to the introduction regarding the importance of having valid risk assessment tools to determine which infants can safely discharge.

8. In the discussion, I would temper language that minimizes the SLE disease activity and medication on maternal and infant infection.

Minor

1. The flow of the results could better match the order of the methods.

2. The clarity could be improved in the first paragraph of the results “Risk of infant infections.”

3. Grammatical error on page 10, line 39: “was too small *to* stratify by preterm birth”

Reviewer	**2**
Name	**Sims, Catherine**
Affiliation	**Duke University**
Date	**15-Sep-2024**
COI	**I am consultant for Amgen and have received previous funding from UCB.**

Really interesting topic and I learned a lot through your explanation of the statistical analysis approach.

The authors are transparent about the limitations of the study including lack of access to lupus activity. I assume this also includes not having access to maternal medications used to treat SLE. One of our biggest fears when using rituximab in the second and third trimesters of pregnancy is risk of B cells depletion in the mother and baby and infections prior to and after delivery. I think this would be an interesting next step to see if medications such as sulfasalazine and hydroxychloroquine contribute less to the risk of maternal and baby infections (compared to biologics and rituximab) and therefore could be a mediating factor in the causal pathway of SLE disease activity, prematurity, and infections in baby.

However, I recognize the importance of the finding that avoiding prematurity should be a clinical focus when treating pregnant women with SLE and the above suggestion is just a next step. Your findings will be of great interest to patients and medical providers treating these high risk patients.

One clarifying question I had is why does the impact of prematurity on infection change in the subanalysis of first birth. My understanding is that the impact of prematurity on infection in the first 3 days decreases from 85% in all births to 59% in first time births and increases from 28% in all births to 77%in first time births in the first year. I found that a bit confusing and was wondering if the authors could expand on that (or if I am misinterpreting the data).

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. April Barnado, Vanderbilt University Medical Center
Comments to the Author:
Gernaat et al. conduct a retrospective cohort study to examine the risk of infection in infants born to SLE mothers compared to infants born to non-SLE mothers and the impact of preterm birth on infection risk. The authors included 1,248 SLE offspring and 34,886 non-SLE offspring from Medical Birth Register. They found higher risk of infection in SLE offspring than non-SLE offspring, particularly in the first 72h after delivery, that was primarily due to preterm birth. They could elaborate on their rationale for using causal mediation analysis and more details on how their control and SLE populations were selected. Overall, this is a relevant and useful topic that I believe many clinicians would be interested in reading.

Thank you for your comments. It is meaningful to us that it is useful information for clinicians. We also appreciate how you have formulated your review in a patient, thoughtful and easy to understand way so that we may improve the manuscript and study for the readers.

We had described on pages 5 and 6 how we identified women and their infants but thanks for pointing out that it could be more detailed. We have added a flowchart (Figure 1) to show the study population selection and added the following text to page 5: “We further restricted the women with SLE to have ≥2 visits listing SLE, at least one of which was required to be given at a department or

specialist that diagnoses, treats or manages SLE (rheumatology, dermatology, nephrology, internal medicine and/or paediatrics). From this population of women with SLE and the general population comparators without SLE, we identified those mothers who gave birth to a liveborn singleton registered in the MBR between March 2006 (as the PDR started in July 2005) and December 2021. A flow chart of the study population selection is depicted in Figure 1." On page 6, we edited the text to make it less repetitive and also added the sentence "There were no general population comparators with an SLE discharge code before pregnancy." This is because we planned on excluding these comparators in case they had an SLE diagnosis since the time between matching and pregnancy may be a long time. However, we found no cases where the comparators had received an SLE code between matching and pregnancy.

We'd also like to provide the reviewer a little background to why the study population was selected this way. We have a data extraction from the Swedish National Board of Health and Welfare of all people with at least one SLE ICD-coded visit in the National Patient Register. We selected controls without SLE matched to this group. We set up this dataset so we could conduct case-control studies looking at risk factors for SLE as well as matched cohort studies looking at outcomes associated with SLE. In all of our studies, we restrict the SLE group to have more strict criteria for inclusion to minimize misclassification of SLE. For the general population, we did not preserve the original matching and kept all comparators who fit our study criteria (having a pregnancy in the medical birth register 2006-2021) because it improves power to have a larger population to compare to the SLE group. We adjusted for the important factors that differ between the two groups that were originally matched on (age and calendar year).

We appreciate the opportunity to make the study selection clearer in the text and hope that this improves the reader's understanding of our approach.

We have added text about the causal mediation analysis on pages 7-8 (please see specific details listed in response to your question #2 below).

Major:
1. Can you give rationale why the 72 hours was used?

An infection in the first 72 hours is the definition of early neonatal sepsis, which has its own clinical applications in terms of infectious agent and pathogenesis. It is associated with serious complications and is more life-threatening than infections later in life. Therefore, we examined this time window to investigate the most clinically relevant and important time window, in consultation with our colleague and co-author who is a paediatrician (Dr. Altman).

We have added text to the bottom of page 6: "We examined infections in the first three days because it has a different pathogenesis than infections later in life and is associated with serious complications that can be life-threatening."

2. I would explain your rationale for using causal mediation analysis, as this technique may not be familiar, particularly to a clinical audience.

Thanks for this suggestion. We have added some text explaining our use of causal mediation analysis on page 7. It now reads: "Mediation analysis can be used to assess factors that are caused by the exposure (maternal SLE) and cause the outcome (infant infection) to better understand the relationship between exposure and outcome and to ultimately identify factors upon which to intervene. Causal mediation analysis accommodates interaction between the exposure and

mediator. We investigated how much of the association between maternal SLE and infant infection operates through the mediating effect of preterm birth."

3. You mention that controls were matched in the database. Did you exclude any conditions in controls, such as other autoimmune diseases?

No, we only selected controls who had no visits listing an SLE ICD code in the National Patient Register before pregnancy. We hope that the new Figure (flow chart) makes it clearer how the controls were matched and what exclusions were made.

4. I would explain why you excluded SLE mothers with only 1 visit for SLE prior to delivery. Are there concerns this was not an accurate diagnosis? If these were true cases is there another rationale for excluding, i.e new diagnosis, incomplete data/missingness?

The reviewer is correct, we excluded mothers who did not have an SLE-coded visit with a specialist before pregnancy because we were concerned about the accuracy of the SLE diagnosis.

A main reason for requiring at least 1 code with a specialist before delivery was to make sure that they had prevalent SLE at the time of delivery and we believe a visit with a specialist which typically diagnoses and/or manages SLE is more accurate. Typically, a patient with SLE in Sweden receives specialist care. There were 41 babies (born to 38 women) who were excluded because they did not have a specialist visit until after the last menstrual period date. 24 of these pregnancies didn't have a specialist visit until after pregnancy. The other 17 had their first specialist visit during pregnancy. These pregnancies could have been included, since it is likely that they are true SLE pregnancies, but they might indicate newly diagnosed SLE, which may have a different effect on pregnancy and infant infection than prevalent SLE under the care of a specialist at the time of pregnancy. However, we doubt that including these few pregnancies would change the results very much.

We have added the numbers describing the exclusion of pregnancies to the flow chart (Figure 1) to be more transparent. Furthermore, we edited the following text on page 6 to explain this exclusion: "Infants born to women with only one visit for SLE before delivery or with no visits with a specialist before pregnancy were excluded to minimise misclassification of maternal SLE."

5. It would be helpful to give more details to justify why only using 2 or more ICD-10 codes for SLE. A reference is given, but it would be helpful to give the PPV or some performance metric of this phenotyping approach. Further, please clarify why the first SLE discharge code was used as a proxy for diagnosis.

The PPV we reported in our previous publication was 97.6% for females with the definition of at least two SLE visits and at least one coded in a specialist clinic, however this was in a study population with a falsely high prevalence (a population enriched with cases). When adjusting the prevalence to be closer to the true prevalence in the population, the PPV is more like 80%. We have not validated this definition in a traditional way by identifying cases and doing a medical record review. This definition is currently being validated and preliminary results show that the PPV is about 88%. We have not validated this definition to identify prevalent SLE during pregnancy. We have added this text to the manuscript along with these caveats.

On page 5, we added the following sentence: "This definition is estimated to have a positive predictive value of 80% in women,(9) but its accuracy has not been evaluated for identifying pregnant women with prevalent SLE."

We added reference #9: Arkema EV, Jonsen A, Rönnblom L, Svenungsson E, Sjöwall C, Simard JF. Case definitions in Swedish register data to identify systemic lupus erythematosus. BMJ Open. 2016; 6:e007769. doi:10.1136/bmjopen-2015-007769

We used the 1st SLE-coded visit as a proxy for diagnosis because that is the first diagnosis we observe in our data, but we have not validated or checked all of the charts to determine if this is the true first date of diagnosis. Because we have excellent coverage of inpatient and outpatient care in all of Sweden over several decades (outpatient care data going back to 2001 and inpatient data since 1964), we are confident that we have identified the first ever *specialist* diagnosis of SLE. We do not have data on primary care where SLE may have first been diagnosed in some cases, but patients with SLE usually receive their diagnosis from specialist care in Sweden. Therefore we believe that our proxy is close to the true date of diagnosis.

We have added the following text on page 6: "The first observed SLE discharge code was used as a proxy for diagnosis date as it is the first observed diagnosis in our data, which does not include primary care. However, SLE diagnosis typically is given by specialists, therefore this is a reasonable proxy. …."

6. Was there any consideration to adjust by gestational age as a continuous variable as opposed to categorical (term, <37 weeks, <32 weeks)?

The reviewer brings up an excellent point since we might have lost information by categorizing gestational age. However, there are some limitations to including continuous gestational age as a mediator in the analysis. This assumes that there is a linear relationship between maternal SLE and gestational age, as well as a linear relationship between gestational age and infant infection. We did not think that for every one week increase in gestational age there would be the same increase in risk of infant infection. We will keep the categorical variable as it is an established cut off in practice, and our results may be more useful to communicate and subgroup infants into high and low risk.

7. Last part of sentence on page 17 first paragraph- "perhaps being extra careful with hospital discharge in first 72h" seems a little strong and vague. We don't know, for example, that hours 72-96 have a decreased rate of infection. The data presented here is for <72h, compared to 30d. As you reference, in clinical practice we divide neonatal sepsis into early onset <72h or late onset 72h-7d of life. Similarly, regarding the comment on page 18 about "early discharge", in the US most term infants are discharged at 48 to 72 hours and early discharge is considered < 48 hours. To your point there are "early-onset sepsis calculators" that can assess risk when considering discharge. It is reasonable to recommend considering SLE as a risk factor when considering early discharge. I would more strongly link your final recommendations to the introduction regarding the importance of having valid risk assessment tools to determine which infants can safely discharge.

Thank you for your comments. We have edited the statements to be clearer and make less of a strong statement:
"Maternal SLE should be considered a risk factor for early neonatal infections and could be used to assess risk when considering early hospital discharge." (page 18).

It was interesting to hear that in the US "early discharge" is considered <48 hours. In Sweden, early discharge is considered before 24 hours, so that is good to know that it has a different meaning in different countries. Most mother and infant pairs are discharged between 24-48 hours in Sweden, but quite a few leave sooner than that, especially if the mother has had previous babies.

8. In the discussion, I would temper language that minimizes the SLE disease activity and medication

on maternal and infant infection.

We have edited the text to read on pages 18-19: “Lupus disease activity and phenotype are strongly related to medication use, and all of these factors could affect infant infection… Future studies should investigate the relationship between SLE-related characteristics and infant infection with more clinically detailed data, with a focus on preterm infants who carry the majority of the risk.”
We have added more text regarding rituximab during pregnancy on page 19, to show that this is a reasonable concern however not in the context of our study. “We do not have information on rituximab use during pregnancy, which depletes B cells in the mother and baby and affects infant infection risk. However, during the study’s time period rituximab was not recommended for use during pregnancy, except in extremely rare cases, according to treatment guidelines by the Swedish Society of Rheumatology. Therefore we do not believe that rituximab has greatly affected our results.”

Minor
1. The flow of the results could better match the order of the methods.
We have edited the results to match the order of the methods.

2. The clarity could be improved in the first paragraph of the results “Risk of infant infections.”
We have edited the paragraph to improve its clarity.

3. Grammatical error on page 10, line 39: “was too small *to* stratify by preterm birth”
We have made the edit to this sentence, thanks for catching this error.

Reviewer: 2
Dr. Catherine Sims, Duke University
Comments to the Author:
Really interesting topic and I learned a lot through your explanation of the statistical analysis approach.

The authors are transparent about the limitations of the study including lack of access to lupus activity. I assume this also includes not having access to maternal medications used to treat SLE. One of our biggest fears when using rituximab in the second and third trimesters of pregnancy is risk of B cells depletion in the mother and baby and infections prior to and after delivery. I think this would be an interesting next step to see if medications such as sulfasalazine and hydroxychloroquine contribute less to the risk of maternal and baby infections (compared to biologics and rituximab) and therefore could be a mediating factor in the causal pathway of SLE disease activity, prematurity, and infections in baby.

Thank you for bringing this up. It was not our intention to study the relationship between SLE medications and infant infection, but rather whether SLE (and all of the things that go along with SLE including medications and disease characteristics) is associated with infant infection.

We do not have information on rituximab and biologics given via infusion in our data as the infusions are given at the hospital and we only have information on prescribed medications dispensed at the pharmacy. However, rituximab and belimumab are used very rarely during conception period and pregnancy in Sweden so we do not believe that this has affected our results. Rituximab was first used in SLE in Sweden in 2001 and not commonly used since then in the SLE population in general, and extremely rare during pregnancy. We have discussed this with our clinical colleagues to get an idea of the number of patients, and over the 15-year period of this study, at the Karolinska Hospital (which sees pregnant SLE patients in the Stockholm region, about 2 million people in the

metropolitan area), they could only think of one pregnant woman with SLE who received rituximab during this period (SLE + lymphoma). Therefore it would be hard to study rituximab and biologics in SLE pregnancy.

We have added a sentence to the limitations section of the discussion to mention this point: "We do not have information on rituximab use during pregnancy, which depletes B cells in the mother and baby and affects infant infection risk. However, during the study's time period rituximab was not recommended for use during pregnancy, except in extremely rare cases, according to treatment guidelines by the Swedish Society of Rheumatology. Therefore we do not believe that rituximab has affected our results"

However, I recognize the importance of the finding that avoiding prematurity should be a clinical focus when treating pregnant women with SLE and the above suggestion is just a next step. Your findings will be of great interest to patients and medical providers treating these high risk patients.

Thank you for understanding that this is one step in a long line of studies and for your encouragement that these findings will be of great interest. We have several ongoing studies examining the relationship between medications and preterm delivery, one of which is currently under review. In that study, we had hoped that HCQ would decrease the risk of preterm delivery but it is not the case. It does, however, decrease preeclampsia risk. This further underscores the fact that preterm delivery is a very heterogenous outcome, with several different causes, and much work remains to find actionable interventions to decrease its occurrence.

One clarifying question I had is why does the impact of prematurity on infection change in the subanalysis of first birth. My understanding is that the impact of prematurity on infection in the first 3 days decreases from 85% in all births to 59% in first time births and increases from 28% in all births to 77% in first time births in the first year. I found that a bit confusing and was wondering if the authors could expand on that (or if I am misinterpreting the data).

Thank you for pointing this out and giving us the opportunity to explain. We believe that one reason for this discrepancy may be the fact that there is less power in the analysis of first-time births. We have added confidence intervals to the proportions in the text and the tables to better display the statistical uncertainty of these estimates. The 85% proportion mediated had a confidence interval of 27 to 144, indicating that preterm birth is a mediator but that the estimate is uncertain. The 59% proportion mediated in first births had a confidence interval of 19 to 98 which overlaps with the estimate from all births.

To reflect the statistical uncertainty in our interpretation of results, we have removed some of the wording that said the proportion mediated was "large" or the emphasis on the exact percentage. We can conclude that there is evidence of mediation due to preterm birth, as expected. We also added the sentence and reference to the discussion on page 19 "Some analyses were limited in power, resulting in wide confidence intervals and the proportion mediated estimates are unstable when sample sizes are small.(24)"

We added reference #24: Mackinnon DP, Warsi G, Dwyer JH. A Simulation Study of Mediated Effect Measures. Multivariate Behav Res. 1995;30(1):41.

Reviewer: 1 competing interests.: None

Reviewer: 2 competing interests.: I am consultant for Amgen and have received previous funding from UCB.