PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study
AUTHORS	Tsao, Nicole; Lynd, Larry; Sayre, Eric; Sadatsafavi, Mohsen; Hanley, Gillian; De Vera, MA

VERSION 1 – REVIEW

REVIEWER	Tsur, Abraham Sheba Medical Center at Tel Hashomer, Obstetrics and Gynecology
REVIEW RETURNED	03-May-2018

GENERAL COMMENTS	In the article entitled "Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study" the authors conclude that use of biologics by women with autoimmune diseases during pregnancy is not associated with an increased risk of serious infections in mothers, during post-partum, or in infants during the first year of life. The topic is very interesting for our readers and has great clinical importance. However, I suggest major revisions to promise the conclusions are based on solid evidence. My main concerns regarding the study design are: 1. (page 14 line 8) - Only singleton pregnancies, 90 women were exposed to biologics, however 100 pregnancies were evaluated. Enrolling the same patients to the study more then once may create many unintended biases. I would recommend selecting randomly only one pregnancy for each patient. 2. (page 16, line 21): TNF-alpha inhibitor biologics (94%) where the most common - I would recommend not to exclude from the analysis patients receiving other biologics that work in a different mechanisms and effect the risk of infection in the mother and newborn differently than TNF-alpha inhibitors. 3. (page 10 line 50-51) Please provide more data on the timing of biologics exposure during pregnancy in the exposed pregnancies, especially how many of the patients were exposed during the last month of pregnancy and what was the neonatal outcome in this sub cohort. Another optional non mandatory suggestion is to report the actual doses used and evaluate the dose response effect. page 11 lines 7&32 - where are supplementary tables 1&2 - I could not find them as part of the PDF and there are no additional files uploaded

REVIEWER	Gene-Siew Ngian Rheumatologist Melbourne Health and Monash Health Australia
REVIEW RETURNED	15-May-2018

GENERAL COMMENTS	Using four linked databases, the authors of this study calculated the adjusted odds ratio of infection requiring hospitalization in women (and their infants) exposed to a biologic during pregnancy and found no increased risk. The strength of the study was the near complete capture of the population where the study was performed. The authors highlight the major limitation of their study which is the small number of exposed patients, with a doubling or tripling of risk still compatible with the upper bounds of their confidence intervals - did they consider looking at serious infections that did not lead to hospitalization? - although the focus of the manuscript was on the complication of infection, did they look at any other outcomes of concern with biologic exposure during pregnancy eg congenital anomalies? - did they collect information on vaccination of infants? I would also be interested in more detail about the duration of exposure in those patients who had a biologic during pregnancy as this have might some effect on risk of infection.

REVIEWER	Annika Montag UCSD, USA
REVIEW RETURNED	08-Jun-2018

GENERAL COMMENTS	The present manuscript “Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study” is a retrospective cohort study exploring associations among receiving a biologics prescription during pregnancy and infections requiring hospitalization in the mother with an autoimmune disease prescribed the biologic and her baby. This paper is an important contribution to the literature as a growing number of pregnant women are exposed to biologics. The conclusions will be comforting to women and their providers: the analysis suggests that exposure and outcome variables are not associated. Furthermore, the manuscript illustrates issues with rare exposure /rare outcome data. Overall comments: 1. Matching procedure must be more clearly defined. In the sensitivity analysis, the “investigator-specified covariates” and “additional factors” used in the propensity score should be specified. What are the unmeasured confounders these are intended to represent? 2. How is disease severity and extent to which the underlying condition is controlled taken into account? Please include in discussion 3. Is there missing data? If yes, how is missing data handled? 4. If data is unavailable regarding harmful perinatal exposures such as smoking and alcohol consumption, please mention in discussion 5. If the sample is limited to women with a hospitalization, are conclusions the same and matching still successful? 6. Where are tables S1 and S2, and Figure 3? Specific comments: Article Summary is not a summary Introduction Pg 7 lines 8-10 – the follow-up timing is unclear. Are mothers followed 42 days or 1 year? Are children followed 28 days or 1 year

	(here and method pg 7 line 48/49 and pg 9 line 28)? Methods Pg 7 lines 24-36 – Four linked databases mentioned but 3 are listed. Should BCPDR be included as follows: “comprised four linked databases including BCPDR and 1) Medical Services…”? Is the 4th Vital Stats? Pg 8 lines 37-40 – “all singleton live born infants…” included, yet table 1 includes stillbirth and delivery with neonatal death Pg 9 line 8 – There is no Table S1 Pg 9 line 50 – how is weight gain dichotomized? (Within recommended guidelines or not? Above or below recommended?) Pg 10, lines 24-29 – Mediators of the effect of exposure. Why are Apgar scores included in analysis when gestational age, birth weight and dysmorphologies are not? Pg 10, lines 46-48 – please show results of bivariate analyses – magnitude of bivariate association. Were covariates added in order based on magnitude of association? Pg 11 lines 10-17 – see overall comment #1. Please clarify matching further. Pg 11, lines 21-24 – Good. Results of match performance evaluation? Results Pg 12, line10 – statistically “more”? Also line 14/15 Pg 12, lines referring to Table 1 – please add significance to table 1 Pg 13, line 14/15 – where is Figure 3? Discussion Consider commenting on the effect of the autoimmune conditions themselves (Figure 2, 3%) and what this means for decision making regarding biologic use in pregnancy. This study adds another piece of data to the risk/benefit analyses women and their providers make when considering biologics during pregnancy. Limitations Consider commenting on the impact of disease severity on results. Also, whether the disease was controlled or not. Were glucocorticoids administered as treatment of maternal disease or to promote fetal lung maturation? If the latter, what are implications? Was maternal asthma treated and, if so, with what medication? Unknown compliance – know prescription was filled but not whether the woman took the medication Perhaps note as limitations that you were unable to control for difficult labors (prolonged, prolonged membrane rupture, multiple vaginal exams or internal fetal monitoring), smoking, stress, …

REVIEWER	Abraham Tsur Stanford University
REVIEW RETURNED	16-Jun-2018

GENERAL COMMENTS	In the article entitled " Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study” the authors investigate retrospectively the association between exposure to biologics during pregnancy and the risk for serious maternal or neonatal infections. The topic is of great clinical importance and relevance and interesting to our readers. However, there are a few major methodologic mistakes that may lead to the wrong conclusions. Therefore, I suggest major revisions before acceptance of the manuscript: Page 8, line 45: Please consider stratifying the biologics exposure based on timing of exposure (trimesters for example) during

	pregnancy. Third trimester exposure may show higher relative risk for serious maternal or neonatal infections. This stratification is especially important for your final conclusion (page 19, line 5) to be valid: “Our findings are compatible with current recommendations where discontinuation of TNF-alpha inhibitor biologics late in the pregnancy could be considered, or if indicated, can be continued throughout the pregnancy” Page 12, line 10: chronic hypertension as well as pre-gestational diabetes (type 1 or 2) should also be included as comorbidities. Page 12, line 38: Please consider reporting also the OR for neonatal infection during the first 3 months of life, which may better capture the effect of biologics treatment during pregnancy on the neonate. Page 14, line 7: there were 90 women exposed to biologics during pregnancy, and 100 babies born to these women. I understand only singleton pregnancies included, therefore some of the women in the exposed group must have had more than one pregnancy. Could you please confirm the patients were treated with biologics during both (or perhaps more than both) the pregnancies? Also does your statistical analysis account for use of dependent variables (the same patient more than once in different pregnancies)? I did not receive the supplementary tables for review.

REVIEWER	Frauke Förger Department of Rheumatology, Immunology and Allergology, University hospital and University of Bern, Switzerland
REVIEW RETURNED	03-Jul-2018

GENERAL COMMENTS	The message is important. The paper is very well done. The retrospective cohort study analyses the association between exposure to biologics during pregnancy and serious infections in mothers and infants. Over the 10-year study period, 90 out of 6218 women were exposed to biologics during pregnancy, with 100 babies born to these women. The analysis showed that there was no association between exposure to biologics and serious maternal postpartum infections or serious infant infections during the first year of life. Comments/ suggestions: -Introduction, page 6: “ …infliximab and adalimumab having higher affitnity for FcRn….”, please cite original articles. - Results, page 12: one outcome parameter was maternal post-partum infection. Serious infections included infection of the amniotic sac and membranes. This is an infection during pregnancy, not post-partum. This infection could be the cause of delivery and could last beyond post-partum. This point should be addressed. -Discussion, page 14 and 16: There is repeated information in the discussion about the findings of other factors independently associated with serious infections in mothers : page 14, line 24-30 and page 16 line 42-48. - Discussion: The authors used drug dispensation data, which does not take into consideration the exact timing of drug exposure in relation to pregnancy. In addition, it remains uncertain whether the prescribed drug was taken by the pregnant women. This limitation should be added in the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Gene-Siew Ngian
Institution and Country: Rheumatologist, Melbourne Health and Monash Health, Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Using four linked databases, the authors of this study calculated the adjusted odds ratio of infection requiring hospitalization in women (and their infants) exposed to a biologic during pregnancy and found no increased risk.

The strength of the study was the near complete capture of the population where the study was performed.

The authors highlight the major limitation of their study which is the small number of exposed patients, with a doubling or tripling of risk still compatible with the upper bounds of their confidence intervals
- did they consider looking at serious infections that did not lead to hospitalization?
Authors: No, the definition for serious infection is one that leads to a hospitalization.

- although the focus of the manuscript was on the complication of infection, did they look at any other outcomes of concern with biologic exposure during pregnancy eg congenital anomalies?
Authors: Other pregnancy related outcomes were assessed in separate studies, some already published (e.g. biologic exposure and preterm delivery and small-for-gestational-age in Annals of the Rheumatic Diseases) or under peer-review.

- did they collect information on vaccination of infants?
Authors: There was no vaccination information available in this dataset

I would also be interested in more detail about the duration of exposure in those patients who had a biologic during pregnancy as this have might some effect on risk of infection.
Authors: Reviewers 4 and 5 similarly brought up this point. We refer Reviewers 1 and 5 to our reply to Reviewer 4's comment below.

Reviewer: 3
Reviewer Name: Annika Montag
Institution and Country: UCSD, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The present manuscript "Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study" is a retrospective cohort study exploring associations among receiving a biologics prescription during pregnancy and infections requiring hospitalization in the mother with an autoimmune disease prescribed the biologic and her baby. This paper is an important contribution to the literature as a growing number of pregnant women are exposed to biologics. The conclusions will be comforting to women and their providers: the analysis suggests that exposure and outcome variables are not associated. Furthermore, the manuscript illustrates issues with rare exposure /rare outcome data.
Overall comments:

1. Matching procedure must be more clearly defined. In the sensitivity analysis, the "investigator-

specified covariates" and "additional factors" used in the propensity score should be specified. What are the unmeasured confounders these are intended to represent?
Authors: We revised the Methods section to be more specific on the procedure for matching without replacement (page 11). In using HDPS, we are attempting to address confounding by indication, which is essentially underlied by health state/disease severity that may be indirectly described by "chains" of proxy variables. For example, the health state of a patient can be assessed through a chain of events consisting of (i) dispensation of a drug that was (ii) prescribed by a physician during a visit who (iii) made a diagnosis because the patient (iv) presented with certain symptoms. Such a chain of proxies corresponds to data captured in multiple dimensions of linked databases and comprise a chain of events that are influenced by access to care, severity of the condition, diagnostic ability of the physician, and preference for one drug over another (Refs: Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data; Epidemiol Camb Mass. 2009 Jul;20(4):512–22; Andersen RM. Revisiting the Behavioral Model and Access to Medical Care: Does it Matter? J Health Soc Behav. 1995;36(1):1–10). As such variables entered into the HDPS included those representing use of medications (e.g. DMARDs, glucocorticoids), comorbidities (e.g., depression), and healthcare utilization (e.g. outpatient visits, prenatal care, laboratory investigations, xrays); we revised Methods to incorporate this (page 11).

2. How is disease severity and extent to which the underlying condition is controlled taken into account? Please include in discussion
Authors: Disease severity and underlying conditions were taken into account with the inclusion of concomitant medications used – e.g., traditional DMARDs and glucocorticoids. In part, the sensitivity analysis using HDPS also takes into account variables that may be associated with disease severity or disease itself.

3. Is there missing data? If yes, how is missing data handled?
Authors: There is no missing data in this dataset because of the administrative nature of the data and that it covers every health service utilized by every resident of the province.

4. If data is unavailable regarding harmful perinatal exposures such as smoking and alcohol consumption, please mention in discussion
Authors: We have added this as a limitation of the study in the Discussion (page 16).

5. If the sample is limited to women with a hospitalization, are conclusions the same
and matching still successful?
Authors: We are afraid that we do not understand this comment. Our study cohort was not limited to women with a hospitalization as the BC Perinatal Database Registry contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in the province of BC from over 60 acute care facilities as well as births occurring at home attended by BC registered midwives. Matching on HDPS was successful.

6. Where are tables S1 and S2, and Figure 3?
Authors: These are provided with this resubmission

Specific comments:

Article Summary is not a summary
Authors: The structure of the article summary follows the instructions for authors from BMJ Open.

Introduction

Pg 7 lines 8-10 – the follow-up timing is unclear. Are mothers followed 42 days or 1 year? Are children followed 28 days or 1 year (here and method pg 7 line 48/49 and pg 9 line 28)?
Authors: This section describes the follow up data available in the BCPDR, however, we do not use this database to ascertain outcomes of serious infections in infants – this comes from ICD codes in the linked discharge abstract database (hospitalizations) during 42 days post-partum for mothers and during the first year of birth for infants. To avoid confusion, we have removed this description of the BCPDR from the Methods section (page 7).

Methods

Pg 7 lines 24-36 – Four linked databases mentioned but 3 are listed. Should BCPDR be included as follows: "comprised four linked databases including BCPDR and 1) Medical Services…"? Is the 4th Vital Stats?
Authors: The BCPDR should be one of the 4 listed, we have clarified this now.

Pg 8 lines 37-40 – "all singleton live born infants…" included, yet table 1 includes stillbirth and delivery with neonatal death
Authors: These refer to 'Prior obstetrical history' as we indicated in bold font in the Table, and not outcomes of the current pregnancy.

Pg 9 line 8 – There is no Table S1
Authors: We have provided this with the resubmission.

Pg 9 line 50 – how is weight gain dichotomized? (Within recommended guidelines or not? Above or below recommended?)
Authors: Maternal weight gain was categorized based on recommended guidelines given BMI at baseline.

Pg 10, lines 24-29 – Mediators of the effect of exposure. Why are Apgar scores included in analysis when gestational age, birth weight and dysmorphologies are not?
Authors: Mediators should not be adjusted as confounders, as such we have not included variables such as gestational age or birth weight. Apgar score is not a predictor of infections or other adverse outcomes post-partum and as such is not a mediator.

Pg 10, lines 46-48 – please show results of bivariate analyses – magnitude of bivariate association. Were covariates added in order based on magnitude of association?
Authors: Reviewer 3 is referring to Methods section and we respectfully disagree that showing results of bivariate is needed. Given the presentation of various statistical models we used in Tables 2 and 3 (including both primary and sensitivity analyses), we think that presenting results of bivariate analyses would be distracting. As we described in Methods, model selection was done by comparing nested models using the Akaike Information Criterion.

Pg 11 lines 10-17 – see overall comment #1. Please clarify matching further.
Authors: We have addressed this in our reply to overall comment #1.

Pg 11, lines 21-24 – Good. Results of match performance evaluation?
Authors: Comparison of the standardized mean differences in baseline characteristics of matched and unmatched cohorts showed successful matching. We did not report this level of detail given that applying HDPS was sensitivity analysis.

Results

Pg 12, line10 – statistically “more”? Also line 14/15
Authors: Please see reply to next comment as they are related we have jointly addressed.

Pg 12, lines referring to Table 1 – please add significance to table 1
Authors: We have revised Table 1 to include an additional column to report p-values for t-tests (differences in means) and Chi-square (differences in proportions) for comparisons between biologics exposed and unexposed. Given this change, we have revised text in the Results to indicate which characteristics were statistically different to address Reviewer 3’s comment above (page 13).

Pg 13, line 14/15 – where is Figure 3?
Authors: We have provided this with the resubmission

Discussion

Consider commenting on the effect of the autoimmune conditions themselves (Figure 2, 3%) and what this means for decision making regarding biologic use in pregnancy.
This study adds another piece of data to the risk/benefit analyses women and their providers make when considering biologics during pregnancy.
Authors: We are unclear on which specific point in “Figure 2, 3%” that Reviewer 3 is pointing to as we reported this in a number of the cells. We feel that we have already stated this potential contribution of the manuscript (e.g., last paragraph of Discussion, page 17).

Limitations
Consider commenting on the impact of disease severity on results. Also, whether the disease was controlled or not.
Authors: We included a sentence in the Discussion of limitations that although we conducted sensitivity analyses involving HDPS approaches, given the inherent limitation with administrative data in that they are not collected for research purposes and thus do not have clinical information to measure disease severity (page 16)

Were glucocorticoids administered as treatment of maternal disease or to promote fetal lung maturation? If the latter, what are implications? Was maternal asthma treated and, if so, with what medication?
Authors: Given the administrative nature of our data, we do not have information on reason for prescriptions. Because we considered it as a comorbidity/covariate, we did not assess treatment of maternal asthma.

Unknown compliance – know prescription was filled but not whether the woman took the medication
Perhaps note as limitations that you were unable to control for difficult labors (prolonged, prolonged membrane rupture, multiple vaginal exams or internal fetal monitoring), smoking, stress, …
Authors: We agree with Reviewer 3’s comment regarding adherence. Nonetheless, research by the EuroMAP Group has shown that pregnant women report taking 43-50% of their prescribed medications, a level of medication adherence consistent with non-pregnant populations, and that adherence tends to be higher (70–100%) for drugs used in the treatment of chronic diseases in this population (Ref: Olesen C, Søndergaard C, Thrane N, Lauge Nielsen G, de Jong-van den Berg L, Olsen J, et al. Do Pregnant Women Report Use of Dispensed Medications? Epidemiology. 2001 Sep;12(5):497). As this point was also brought up by Reviewer 5, we have added this point to the Discussion of limitations (page 16). Related to this since suggested revisions to incorporate limitations have made this section quite lengthy, we have split the paragraph originally describing strengths and limitations into 2 respective paragraphs (page 16).

Reviewer: 4
Reviewer Name: Abraham Tsur
Institution and Country: Stanford University
Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below
In the article entitled " Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study" the authors investigate retrospectively the association between exposure to biologics during pregnancy and the risk for serious maternal or neonatal infections. The topic is of great clinical importance and relevance and interesting to our readers. However, there are a few major methodologic mistakes that may lead to the wrong conclusions. Therefore, I suggest major revisions before acceptance of the manuscript:

Page 8, line 45: Please consider stratifying the biologics exposure based on timing of exposure (trimesters for example) during pregnancy. Third trimester exposure may show higher relative risk for serious maternal or neonatal infections. This stratification is especially important for your final conclusion (page 19, line 5) to be valid: "Our findings are compatible with current recommendations where discontinuation of TNF-alpha inhibitor biologics late in the pregnancy could be considered, or if indicated, can be continued throughout the pregnancy"
Authors: We appreciate Reviewer 4's suggestion and have actually conducted analyses according to trimesters. However, given the small numbers (due to 'rare exposure', 'rare outcome') that we observed in our cohort, some of the statistical models did not converge. We do think that this is important potential future work as more data accumulates over time, which we hope to do. As a similar point regarding duration of use during pregnancy was brought up Reviewer 1 above, if interested, we have published a prior descriptive study of patterns of biologic use and discontinuation before and during pregnancy in the same cohort of women with autoimmune disease (Ref: Tsao et al. Arthritis Care & Res 2018;70(7):979-86)) where we showed higher proportions of women discontinuing their biologic with increasing trimester of pregnancy. We also referred to this paper in the Discussion (page 16) and surmise that fewer women being exposed close to delivery may be an explanation of low numbers of outcomes we observed.

Page 12, line 10: chronic hypertension as well as pre-gestational diabetes (type 1 or 2) should also be included as comorbidities.
Authors: Following Reviewer 4's suggestion, we conducted additional analyses to create variables representing chronic hypertension and diabetes mellitus. We made corresponding revisions in the Methods (page 10) and Table 1 (page 24). We conducted bivariate analyses with our study outcomes. For maternal post-partum serious infections, univariate odds ratios (OR) and 95% confidence intervals (CI) are for diabetes, 0.95 (0.58 to 1.54) and hypertension, 0.98 (0.67 to 1.42). For infant serious infections, univariate ORs and 95% CI are for diabetes, 1.48 (1.06 to 2.07) and for hypertension, 1.14 (0.85 to 1.53). When we entered diabetes into the multivariable model, the adjusted OR was 1.18 (0.83 to 1.67) and the Akaike Information Criterion (AIC) was higher than the AIC in our reported multivariable model (Model 2).

Page 12, line 38: Please consider reporting also the OR for neonatal infection during the first 3 months of life, which may better capture the effect of biologics treatment during pregnancy on the neonate.
Authors: Unfortunately, given the small number of infant serious infections we are not able to. Our data sharing agreements require adherence to strict rules regarding reporting and disclosing information on small cell sizes.

Page 14, line 7: there were 90 women exposed to biologics during pregnancy, and 100 babies born to

these women. I understand only singleton pregnancies included, therefore some of the women in the exposed group must have had more than one pregnancy. Could you please confirm the patients were treated with biologics during both (or perhaps more than both) the pregnancies? Also does your statistical analysis account for use of dependent variables (the same patient more than once in different pregnancies)?
I did not receive the supplementary tables for review.
Authors: As we described in Methods (page 8), the unit of analysis was pregnancy and we confirm that women with more than one pregnancies were treated with biologics during all included pregnancies. We also described in Methods (page 10) that although we used approaches (multivariable regression analyses using generalized estimating equation models with logit link and clustered by mother) to account for multiple pregnancies in the same woman, the models did not converge. But nonetheless, previous work on a larger sample from our source population showed that accounting for correlations between multiple pregnancies within the same woman did not appreciably change effect estimates and confidence intervals.

Reviewer: 5
Reviewer Name: Frauke Förger
Institution and Country: Department of Rheumatology, Immunology and Allergology, University hospital and University of Bern, Switzerland
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
The message is important. The paper is very well done.
The retrospective cohort study analyses the association between exposure to biologics during pregnancy and serious infections in mothers and infants. Over the 10-year study period, 90 out of 6218 women were exposed to biologics during pregnancy, with 100 babies born to these women. The analysis showed that there was no association between exposure to biologics and serious maternal postpartum infections or serious infant infections during the first year of life.
Comments/ suggestions:
-Introduction, page 6: " …infliximab and adalimumab having higher affitnity for FcRn….", please cite original articles.
Authors: Done

- Results, page 12: one outcome parameter was maternal post-partum infection. Serious infections included infection of the amniotic sac and membranes. This is an infection during pregnancy, not post-partum. This infection could be the cause of delivery and could last beyond post-partum. This point should be addressed.
Authors: We took this point into account. As described in Methods (page 9), serious post-partum infections were defined as any episode of hospitalization, including the delivery episode until 42 days post-partum – the conventional definition for post-partum period of concern.

-Discussion, page 14 and 16: There is repeated information in the discussion about the findings of other factors independently associated with serious infections in mothers : page 14, line 24-30 and page 16 line 42-48.
Authors: We deleted the last sentence in the paragraph 1 of Discussion (page 14) so there is no repeated information.

- Discussion: The authors used drug dispensation data, which does not take into consideration the exact timing of drug exposure in relation to pregnancy. In addition, it remains uncertain whether the prescribed drug was taken by the pregnant women. This limitation should be added in the discussion.
Authors: Reviewers 1 and 4 similarly brought up this point. Please see our response and corresponding revisions.

VERSION 2 – REVIEW

REVIEWER	Abraham Tsur Stanford University, California, USA
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	Well done. Thank you for addressing my concerns.

REVIEWER	Gene-Siew Ngian Rheumatologist Melbourne Health and Monash Health Australia
REVIEW RETURNED	25-Sep-2018

GENERAL COMMENTS	Thank you for addressing my query about duration of exposure to biologic agent during pregnancy and for referring to your previous work regarding this issue (Tsao et al. Arthritis Care & Res 2018;70(7):979-86). If you have data on discontinuation rates in the cohort included in the current study, I think it would be worth reporting briefly and then mentioning in your Discussion that this should be taken into account when interpreting your conclusions.

REVIEWER	Frauke Förger University of Bern Switzerland
REVIEW RETURNED	13-Sep-2018

GENERAL COMMENTS	I am fine with the changes that were made.

VERSION 2 – AUTHOR RESPONSE

Revision requested by Reviewer 2:
Thank you for addressing my query about duration of exposure to biologic agent during pregnancy and for referring to your previous work regarding this issue (Tsao et al. Arthritis Care & Res 2018;70(7):979-86). If you have data on discontinuation rates in the cohort included in the current study, I think it would be worth reporting briefly and then mentioning in your Discussion that this should be taken into account when interpreting your conclusions.

Author response:
The previous work cited is actually done on the same cohort, as such we have clarified this in the discussion section of the current paper (page 16).