OBSTETRICS & GYNECOLOGY

Date: Dec 20, 2019
To: "Emily A Peterson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2213

RE: Manuscript Number ONG-19-2213

Rheumatologic Medication Use During Pregnancy: A Review

Dear Dr. Peterson:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Comments to the author:

The authors present a review article looking at common rheumatologic conditions and medication classification in pregnancy. They address a very important, and antiquated, system of drug classification on a continuous risk scale of A-X. There has been more than a decade long struggle to move away from this system with little success. I think this manuscript addresses many of the short comings of the old classification system along with a review of the new recommendation for drug classification with a specific focus on rheumatologic diseases.

My only suggestion would be to review the old system with examples of why there needs to be a reassessment. Examples like OCP being cat X. Although some animal studies there are no human studies showing teratogenicity with an emphasis of risk vs. benefits which is otherwise more applicable to category C. Given there is no benefit to contraception in pregnancy this is the reported relegation to Cat X. Pharmacoepidemiol Drug Saf. 2013 Sep; 22(9): 1013-1018. The cited article also describes the Teratology Information System rating (TERIS) which is clinically useful and may be helpful to incude in the review.

Abstract: Well written and concise
Line 133-134 Although the impact of pregnancy on any chronic medical condition is important, I think the rewording of the effect of rheumatologic disease on pregnancy is of greater interest to the audience. This also is in alignment with the in depth discussion of FDA classification of medication in pregnancy and lactation.

Introduction:
Line 156-163 The gist of the paragraph seems to be a broad overview of the effect of pregnancy on the disease and visa versa. I would suggest stating that some diseases, like RA, may improve however other conditions like SLE, AS and IBD may worsen, particularly if there is active disease during pregnancy. This may better articulate the shared decision making when looking at treatment options and medications.

Linw 168 This is where I would suggest giving examples of the misleading use of categorical risk A-X.

Line 173 Expand upon how the old categorization system is updated when there is new or out dated information. Where is this coming from and how does the FDA incorporate and disseminate this information and labeling?

Line 175-181 Describe the EULAR and BSR guidelines and principles in using antirheumatic drugs in pregnancy? Is it similar to the shared decision model described in this manuscript?

NSAIDS
Line 200-201 Spontaneous abortion and miscarriage are the same thing. This is redundant unless there was a different meaning.

Glucocorticoids

Line 211-213 I would recommend using reduce preterm complications and morbidity in preterm deliveries vs. prevention.

Others suggestion would be to comment on risk of gestation diabetes. BMC Pregnancy Childbirth. 2019 May 22;19(1):179. doi: 10.1186/s12884-019-2329-0.

DMARDS

Line 282 Describe what are acceptable forms of dual contraceptives. The citation #52 is from the package insert. With highly effective LARC what additional contraceptive is recommended?

Biologics
Line 433-434 Expand upon the timing of IgG transfer and need to delay neonatal live vaccines. This is a very important teaching point.

Breastfeeding
Line457-458 The majority of antibodies in breast milk are IgA. Even though some IgG can pass, the presence of AntiTumor necrosis factor medications may have come from use in later pregnancy passing transplacentally vs. via breast milk.

Discussion:
This is a good review of the data and a shared decision making model in a multi disciplinary framework.

The tables are a concise summary of the different categories of medications, classification in pregnancy and breast feeding.

Reviewer #2: Emily Peterson and her team from the University of Iowa present a review article focusing on the use of medications for rheumatologic disorders and how these medications may impact pregnancy outcomes. They include a very thorough list of medications from a wide number of medication classes. Their interpretation of the literature is largely evidence-based and primarily is focused on the association of rheumatologic medications with first trimester spontaneous abortion or congenital anomalies. The review also provides a nice summary for the obstetrician-gynecologist on mechanism of action of many of these medications and addresses newer medications that obstetrician-gynecologists may not be familiar with.

Specific questions or comments for the authors:

1. My familiarity with azathioprine is primarily in the pregnant inflammatory bowel disease (IBD) patient population. In the pregnant IBD population, my understanding is that abrupt cessation of azathioprine is associated with IBD relapse, that is then difficult to control. As IBD flares are associated with adverse pregnancies outcomes such as low birth weight and preterm delivery, our recommendation to pregnant women with IBD who are on azathioprine is to remain on the medication. When rheumatologic patients abruptly stop azathioprine, is there a similar concern for relapse? If so, do you feel that the disease relapse may have a greater impact on the pregnancy than potential risks for remaining on the medication, and as such, is the recommendation to discontinue the medication warranted?

2. Your review primarily focuses on the association of rheumatologic medications with congenital anomalies and first trimester spontaneous abortion. In the discussion section, you state briefly (lines 510-511), that discontinuation of medications may result in a flare, which could impact the pregnancy. This is an important concept. With many of the medications (clearly not methotrexate), active disease may pose a greater risk to the pregnancy than the medication does. As such, similar to that comment presented in Number 1 above, I feel that your paper would be strengthened by reviewing data demonstrating how medication discontinuation of certain drugs, may result in disease relapse and that disease relapse may drive pregnancy complications such as preeclampsia, preterm labor, fetal growth restriction, and/or preterm delivery, which could potentially have a greater impact on the pregnancy than the medication would.

3. The short title uses the abbreviation, DMARD. This abbreviation is likely not well-known to the Ob/gyn community. Would you consider revising your short title?

4. TNF Inhibitors - Infliximab and adalimumab. My group's practice is to continue infliximab and adalimumab through the entire second trimester and most of the third trimester. Your paper suggests (line 429) that these medications should be discontinued at 20 weeks' gestation. Despite their ability to cross the placenta, there is good data, at least in the IBD population, that the use of these medications through the second and early third trimester, do not impact a neonate's

ability to respond to vaccine (live-vaccines are still to given until one year old) and also are not associated with an increased risk for infection in the first year of life. Again, I worry about recommendations to discontinue these drugs at 20 weeks and the risk for disease relapse. Disease relapse may then lead to a poor pregnancy outcome. Next, due to risk for developing autoantibodies to these medications, we do not recommend stopping infliximab or adalimumab in women who have good disease control, and then switching to certolizumab during the pregnancy for the sole purpose that it does not cross the placenta (antibody lacks the Fc portion). Are the recommendations to discontinue infliximab and adalimumab at 20 weeks in the rheumatologic population warranted?

5. A descripton of the search strategy used to idenfity the included studies is not provided.

Reviewer #3: Rheumatologic medication during pregnancy: A review by Peterson et al., is a good summary on the latest update on immunosuppression medication in pregnancy and breastfeeding. It is not a systematic review.

Introduction

The statement about the effect of systemic lupus erythematous (SLE) on pregnancy is a bit simplistic and undermines the complexity of caring for women with SLE while pregnant (Line 159).

The statement beginning with without knowing… (line 159-160) should be taken out, since we do have predictors such as disease activity before pregnancy and other known predictors of morbidity that may help predict which pregnancies are more at risk.

The authors describe the length that the FDA went to with their update that goes beyond using the A-X categories, but then they went ahead and used these categories while describing older medications. They should stay away from these categories and only use description.

In the glucorticoids section, the discuss the incidence of cleft palate and state that the incidence may be increased (line 214). I suggest that they include the absolute number that shows that although it may be increased it is still small and may be acceptable.

For azathioprine, the authors should state that the increases in rates of prematurity and birth weight may also be related to the severity of maternal disease (line 234).

For the section on rituxan, they should state that the medication could be used for life threatening maternal conditions that may require it.

The same should be stated for the TNF inhibitors. If the maternal condition requires it to be continued because of the severity of maternal disease, they could be continued during pregnancy if the benefits outweigh the risks for the foetus after discussion between the patient and care providers.

The breastfeeding information should be included after each section of the medication discussed. They should describe what is the acceptable amount of medication in breastmilk according to the American Pediatric Association.

Discussion

Line 511 describes the impact of discontinuation of medication. This has been well documented in lupus and this should be stated.

The effect on pregnancy if the male partner is taking these medications should also be discussed.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and

you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

10. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

11. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

Nancy C Chescheir, MD

Editor-in-Chief

Obstetrics and Gynecology

1/6/2020

Dear Dr. Chescheir,

Thank you for the opportunity to revise our manuscript, “Rheumatologic Medication Use During Pregnancy: A Review.” We appreciate the comments and suggestions from the reviewers and have included our responses below. We hope you will favorably consider our manuscript for publication in Obstetrics and Gynecology.

This manuscript has not been published and is not under consideration for publication elsewhere. It will not be

Please see below comments by reviewers in addition to our responses.

Thank you for your consideration of our manuscript. We look forward to hearing from you.

Sincerely,

Emily Peterson, PharmD

Reviewer #1: Comments to the author:

The authors present a review article looking at common rheumatologic conditions and medication classification in pregnancy. They address a very important, and antiquated, system of drug classification on a continuous risk scale of A-X. There has been more than a decade long struggle to move away from this system with little success. I think this manuscript addresses many of the short comings of the old classification system along with a review of the new recommendation for drug classification with a specific focus on rheumatologic diseases.

My only suggestion would be to review the old system with examples of why there needs to be a reassessment. Examples like OCP being cat X. Although some animal studies there are no human studies showing teratogenicity with an emphasis of risk vs. benefits which is otherwise more applicable to category C. Given there is no benefit to contraception in pregnancy this is the reported relegation to Cat X. Pharmacoepidemiol Drug Saf. 2013 Sep; 22(9): 1013-1018. The cited article also describes the Teratology Information System rating (TERIS) which is clinically useful and may be helpful to incude in the review. **Examples were added, please see line 107-110 (under the all markup view, view on word with track changes showing).**

Abstract: Well written and concise

Line 133-134 Although the impact of pregnancy on any chronic medical condition is important, I think the rewording of the effect of rheumatologic disease on pregnancy is of greater interest to the audience. This also is in alignment with the in depth discussion of FDA classification of medication in pregnancy and lactation. **This line was re-worded to "the impact rheumatic disease has on pregnancy" to be in line with the obstetric audience that the paper is intended for. Please see lines 66-67 (under the all markup view)**

Introduction:

Line 156-163 The gist of the paragraph seems to be a broad overview of the effect of pregnancy on the disease and visa versa. I would suggest stating that some diseases, like RA, may improve however other conditions like SLE, AS and IBD may worsen, particularly if there is active disease during pregnancy. This may better articulate the shared decision making when looking at treatment options and medications. **The paragraph already articulates that some rheumatologic diseases may worsen in pregnancy while others may improve. Irritable bowel Disease was not included as this is not a rheumatologic disease and is thus outside the scope of this review. An additional sentence about the importance of shared decision making was added to the introduction. The conclusion already contains information about the increased risk to the pregnancy if autoimmune disease (SLE and RA are discussed specifically) are active at time of conception.**

Linw 168 This is where I would suggest giving examples of the misleading use of categorical risk A-X. **Azathioprine example was added, please see line 107-110 (under the all markup view).**

Line 173 Expand upon how the old categorization system is updated when there is new or out dated information. Where is this coming from and how does the FDA incorporate and disseminate this information and labeling? **Information was added to explain this more. Please see lines 115-120 (under the all markup view)**

Line 175-181 Describe the EULAR and BSR guidelines and principles in using antirheumatic drugs in pregnancy? Is it similar to the shared decision model described in this manuscript? **Summarizing the EULAR and BSR guidelines in detail cannot be done within the word limit of this paper. The references to these guidelines were provided and they can be perused at length if desired by the reader. The purpose of this paragraph is to make the reader aware of the existence of these guidelines so that if further information is needed, they can easily access this reliable information. We did add in a few additional sentences which briefly summarize the task undertaken by each of these guidelines. (see paragraph 3 of introduction).**

NSAIDS

Line 200-201 Spontaneous abortion and miscarriage are the same thing. This is redundant unless there was a different meaning. "**spontaneous abortion" was removed from this line - see new line 152 (under all markup view)**

Glucocorticoids

Line 211-213 I would recommend using reduce preterm complications and morbidity in preterm deliveries vs. prevention. **This line was updated as requested. See new line 163-164 (under all markup view).**

Others suggestion would be to comment on risk of gestation diabetes. BMC Pregnancy Childbirth. 2019 May 22;19(1):179. doi: 10.1186/s12884-019-2329-0. **A sentence was added to the end of line 171 Under all markup view).**

DMARDS

Line 282 Describe what are acceptable forms of dual contraceptives. The citation #52 is from the package insert. With highly effective LARC what additional contraceptive is recommended? **Please see updated wording of this section, line 236-241 (under all markup view).**

Biologics

Line 433-434 Expand upon the timing of IgG transfer and need to delay neonatal live vaccines. This is a very important teaching point. **Revisions were made to lines 396-399 (under all markup view) to include more information specific to IgG transfer**

Breastfeeding

Line457-458 The majority of antibodies in breast milk are IgA. Even though some IgG can pass, the presence of AntiTumor necrosis factor medications may have come from use in later pregnancy passing transplacentally vs. via

breast milk. **We have added a statement into the 3rd paragraph of the Breastfeeding section (line 425 under all markup view) to acknowledge that most antibodies in breastmilk are IgA, but some IgG can pass. We did not state the presence of anti-tumor necrosis factor medications in infant serum may have come from transplacental use vs via breastmilk as this is a theory. The paper does acknowledge that transplacental passage of TNF inhibitors occurs during the second and third trimesters in the section above entitled "Tumor Necrosis Factor Inhibitors.".**

Discussion:

This is a good review of the data and a shared decision making model in a multi disciplinary framework.

The tables are a concise summary of the different categories of medications, classification in pregnancy and breast feeding.

Reviewer #2: Emily Peterson and her team from the University of Iowa present a review article focusing on the use of medications for rheumatologic disorders and how these medications may impact pregnancy outcomes. They include a very thorough list of medications from a wide number of medication classes. Their interpretation of the literature is largely evidence-based and primarily is focused on the association of rheumatologic medications with first trimester spontaneous abortion or congenital anomalies. The review also provides a nice summary for the obstetrician-gynecologist on mechanism of action of many of these medications and addresses newer medications that obstetrician-gynecologists may not be familiar with.

Specific questions or comments for the authors:

1. My familiarity with azathioprine is primarily in the pregnant inflammatory bowel disease (IBD) patient population. In the pregnant IBD population, my understanding is that abrupt cessation of azathioprine is

associated with IBD relapse, that is then difficult to control. As IBD flares are associated with adverse pregnancies outcomes such as low birth weight and preterm delivery, our recommendation to pregnant women with IBD who are on azathioprine is to remain on the medication. When rheumatologic patients abruptly stop azathioprine, is there a similar concern for relapse? If so, do you feel that the disease relapse may have a greater impact on the pregnancy than potential risks for remaining on the medication, and as such, is the recommendation to discontinue the medication warranted? **This is an excellent point and is discussed in the first paragraph of the conclusion with the statement, "...we recommend immediate consultation with Rheumatology and OB prior to discontinuing medication, as discontinuation may pose a significant risk for maternal disease flare, which may carry a greater risk to the fetus than continuation of the medication. Discontinuation of medication because of pregnancy in patients with rheumatoid arthritis has been found to be associated with a significantly earlier gestational age at delivery, further underscoring the importance of careful discussion surrounding medication discontinuation."**

2. Your review primarily focuses on the association of rheumatologic medications with congenital anomalies and first trimester spontaneous abortion. In the discussion section, you state briefly (lines 510-511), that discontinuation of medications may result in a flare, which could impact the pregnancy. This is an important concept. With many of the medications (clearly not methotrexate), active disease may pose a greater risk to the pregnancy than the medication does. As such, similar to that comment presented in Number 1 above, I feel that your paper would be strengthened by reviewing data demonstrating how medication discontinuation of certain drugs, may result in disease relapse and that disease relapse may drive pregnancy complications such as preeclampsia, preterm labor, fetal growth restriction, and/or preterm delivery, which could potentially have a greater impact on the pregnancy than the medication would. **Please see above response to Reviewer #2's first comment. In addition, this is further addressed in the 2nd paragraph of the conclusion as well. We have also added a short discussion on risk/benefit of medication discontinuation under the "Tumor Necrosis Inhibitor" section (see lines 393 to 396 under all markup view).**

3. The short title uses the abbreviation, DMARD. This abbreviation is likely not well-known to the Ob/gyn community. Would you consider revising your short title? **DMARD was spelled out in the short title.**

4. TNF Inhibitors - Infliximab and adalimumab. My group's practice is to continue infliximab and adalimumab through the entire second trimester and most of the third trimester. Your paper suggests (line 429) that these medications should be discontinued at 20 weeks' gestation. Despite their ability to cross the placenta, there is good data, at least in the IBD population, that the use of these medications through the second and early third trimester, do not impact a neonate's ability to respond to vaccine (live-vaccines are still to given until one year old) and also are not associated with an increased risk for infection in the first year of life. Again, I worry about recommendations to discontinue these drugs at 20 weeks and the risk for disease relapse. Disease relapse may then lead to a poor pregnancy outcome. Next, due to risk for developing autoantibodies to these medications, we do not recommend stopping infliximab or adalimumab in women who have good disease control, and then switching to certolizumab during the pregnancy for the sole purpose that it does not cross the placenta (antibody lacks the Fc portion). Are the recommendations to discontinue infliximab and adalimumab at 20 weeks in the rheumatologic population warranted? **Additional information has been added to this paragraph specifically addressing the clinical knowledge and the common practice for continuation of these agents throughout pregnancy (see lines 393 to 399 under all markup view)**

5. A descripton of the search strategy used to idenfity the included studies is not provided. **This paper is a general review of the literature. It is not a systematic review.**

Reviewer #3: Rheumatologic medication during pregnancy: A review by Peterson et al., is a good summary on the latest update on immunosuppression medication in pregnancy and breastfeeding. It is not a systematic review.

Introduction

The statement about the effect of systemic lupus erythematous (SLE) on pregnancy is a bit simplistic and undermines the complexity of caring for women with SLE while pregnant (Line 159). **A short statement was added here to highlight the challenge of caring for these patients. The challenge of caring for patients with SLE is elaborated on more specifically in paragraph 2 of the conclusion.**

The statement beginning with without knowing… (line 159-160) should be taken out, since we do have predictors such as disease activity before pregnancy and other known predictors of morbidity that may help predict which pregnancies are more at risk. **We have changed this statement to: "Healthcare professionals should take into account common behaviors of the underlying rheumatologic disease during pregnancy, current disease control, and the patient's disease severity to help predict how a woman's rheumatic disease will respond to her pregnancy and to help guide discussions about therapy options during pregnancy." See lines 93-96 under all markup view**

The authors describe the length that the FDA went to with their update that goes beyond using the A-X categories, but then they went ahead and used these categories while describing older medications. They should stay away from these categories and only use description. **Since some medications have not yet been updated to the new system, and the package insert still lists the categories, we decided to include these. We have added a comment to the end of the introduction to address this. Please see line 118-120 (under all markup view)**

In the glucorticoids section, the discuss the incidence of cleft palate and state that the incidence may be increased (line 214). I suggest that they include the absolute number that shows that although it may be increased it is still small and may be acceptable. **We have added a sentence at the end of line 166 (under all mark up view) to address this.**

For azathioprine, the authors should state that the increases in rates of prematurity and birth weight may also be related to the severity of maternal disease (line 234). **This is a very good point that was missed. We have added a sentence to address this. Please see lines 189-191 (under all markup view).**

For the section on rituxan, they should state that the medication could be used for life threatening maternal conditions that may require it. **A risk vs benefit statement has been added to the rituximab section. Please see line 307-309 (under all markup view)**

The same should be stated for the TNF inhibitors. If the maternal condition requires it to be continued because of the severity of maternal disease, they could be continued during pregnancy if the benefits outweigh the risks for the foetus after discussion between the patient and care providers. **Additional information has been added to this section to address this concern. Please see lines 393-399 (under all markup view).**

The breastfeeding information should be included after each section of the medication discussed. They should describe what is the acceptable amount of medication in breastmilk according to the American Pediatric Association. **We appreciate this suggestion, however we felt re-organizing the paper in this way would significantly increase the word count and would potentially be difficult for the reader to follow. The table helps to serve as a quick reference where information about pregnancy and lactation are summarized for each drug. The American Academy of Pediatrics has not published an acceptable amount of medication in breastmilk, as this would vary widely according to the medication, age of the infant, and other comorbidities of the infant. NIH maintains the LactMed database with detailed information about levels of each drug found in infant serum and possible adverse effects. We have included this resource within the manuscript for readers who seek additional information.**

Discussion

Line 511 describes the impact of discontinuation of medication. This has been well documented in lupus and this should be stated. **This is discussed further in the next paragraph of the discussion, specifically pertaining to lupus. We have also added additional information about this in the "Azathioprine" section: "numerous studies have shown active lupus during pregnancy can be associated with fetal loss, prematurity and low birth weight."**

The effect on pregnancy if the male partner is taking these medications should also be discussed. **We agree that medication use in the male partner can have important effects on pregnancy, however this is outside the scope of this paper. Due to space constraints we cannot include this information in this review. However if this topic is of interest, we would be very happy to write a subsequent review that specifically addresses this topic.**