Author’s response to reviews

Title: Pregnancy Outcomes in Women with Kidney Transplant: Metaanalysis and Systematic Review

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The authors would like to thank the editors and reviewers for their valuable comments. Please find the author responses below.

Editor Comments:

The topic of the present metanalysis is of great interest. Pregnancy in kidney transplant patients is a very important achievement for transplanted women but it is also quite controversial. The Authors have done a very hard work in identifying studies from 1947 through 2017, however this is surely a point of weakness of the study since, as underlined by both the reviewers, it is not possible to compare kidney transplantation and obstetric care in such a big period of time. Probably, as suggested by one of the reviewers the authors should discuss data before the 2000 in
a separate paper. The paper also lack of novelty since a similar work on pregnancy and transplantation has already been published by Deshpande.

Thank you for this valuable suggestion.

As mentioned by the reviewers, the better study design would be to look at data in the recent decade. Although we searched for studies from various data search engines from their date of inception through 2017, published studies that were found to be eligible were from 1980-2017, and were included. The year of publication of the study is not correlated with the year in which they received kidney transplants. For example, majority of studies published after 2000 have study population that spans prior to 2000.

As suggested by reviewers, we performed a sub-group analysis of published studies 2000-2017. The results of the subgroup analysis were consistent with the study results. We would like to clarify that majority of published studies after 2000 had patients before 2000 included in their study population. Due to overlapping decades in the various studies, the results of the sub analysis have to be interpreted keeping this limitation in mind. We have added the subgroup analysis in the supplement.

It is expected for the outcomes to change due to improvement in obstetric care in kidney transplant recipients over the course of time. However, due to the above mentioned limitations of the various studies, where it is not possible to separate the pregnancies in kidney transplant recipients by decades, this remains the weakness of the study. We have added this in the limitation section.

BMC Nephrology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Giorgina Barbara Piccoli (Reviewer 1): The authors made a great effort in updating a systematic review on pregnancy after kidney transplantation; I have however some major points to make:

1. the novelty also with respect to the famous and very well done systematic review by Deshpande should be clearly highlighted: why do we need a new systematic review? (I agree that this is very useful, but this should be clearly stated)
Thank you for this valuable suggestion. We have revised the introduction and emphasized on the novelty of study. To the best of our knowledge, no metaanalysis on post-kidney transplant pregnancy outcomes has been published in the last few years. Our analysis was more comprehensive, and used PubMed/MEDLINE, Elsevier EMBASE, Scopus, BIOSIS Previews, ISI Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials (CENTRAL) for search engines.

“Data on clinical outcomes of pregnancy in kidney transplant recipients is limited from case reports, single-center studies, and voluntary registries. The usefulness of the voluntary registries is further limited due to underreporting and incomplete data capture. To the best of our knowledge, no comprehensive metaanalysis on post-kidney transplant pregnancy outcomes has been performed in the recent years. Since kidney transplant is common in women of child bearing age and most of the data on outcomes of pregnancy comes from these retrospective studies, our metaanalysis is both timely and important. The comprehensive analysis of various worldwide registries, single-center studies, and case series will provide generalizable inferences about post-kidney transplant pregnancy outcomes, and help guide the pregnancy in kidney transplant recipients”

2. On the account of the deep changes in indications, follow-up and maternofoetal care I strongly argue that a systematic review has no advantage of staring since 1947; would the authors like to discuss data before 2000, it should be done separately and not included into the present review

Thank you for this valuable suggestion.

As mentioned by the reviewers, the better study design would be to look at data in the recent decade. Although we searched for studies from various data search engines from their date of inception through 2017, published studies that were found to be eligible were from 1980-2017, and were included. The year of publication of the study is not correlated with the year in which they received kidney transplants. For example, majority of studies published after 2000 have study population that spans prior to 2000.

As suggested by reviewers, we performed a subgroup analysis of published studies 2000-2017. The results of the subgroup analysis were consistent with the study results. We would like to clarify that majority of published studies after 2000 had patients before 2000 included in their study population. Due to overlapping decades in the various studies, the results of the sub analysis have to be interpreted keeping this limitation in mind. We have added the subgroup analysis in the supplement.

It is expected for the outcomes to change due to improvement in obstetric care in kidney transplant recipients over the course of time. However, due to the above mentioned limitations of
the various studies, where it is not possible to separate the pregnancies in kidney transplant recipients by decades, this remains the weakness of the study, and we have added this in the limitation section.

3. All systematic reviews should be recorded in a database; did the authors do it?

We recorded the systemic review in a database.

4. The review should follow the MOOSE criteria; a statement should be added; I did not find the MOOSE table in the attachment

We instead used the PRISMA criteria to conduct meta-analysis. We have mentioned this in the methodology. The study design figure is according to the PRISMA criteria (http://annals.org/aim/fullarticle/744664/preferred-reporting-items-systematic-reviews-meta-analyses-prisma-statement).

“We performed a systematic review and meta-analyses reported according to PRISMA guidelines for studies exploring incidence and outcomes of pregnancy in women with kidney transplant (Figure 1).”

5. The authors should be highly cautious in drawing conclusions on miscarriages (reporting bias very likely)

Thank you for the suggestion. We have added that there could be a reporting bias in miscarriage rate, which remains a limitation.

6. I suggest changing the heading on "ideal age" in age at conception; such a heading may be misleading

We have removed the word ideal and changed it to “maternal age at conception”.

7. The discussion is very long; the novelty of the study is not evident

We have shortened the discussion. We have focused on the novel findings of the study including the rates of gestational diabetes, higher rates of still birth and neonatal mortality, and favorable fetal outcomes in < 2 year time period.
8. The difficulties in classifying superimposed preeclampsia should be highlighted

We have highlighted the difficulty in superimposed preeclampsia in the discussion section.

“Hypertension is common in kidney transplant recipients prior to conception with a reported incidence of 52% to 69%. Several factors can contribute to the onset of hypertension after renal transplantation, including but not limited to the type of immunosuppressive therapy (calcineurin inhibitors and corticosteroids), allograft function, donor type, obesity, alcohol, smoking, and presence of a native kidney (increased production of renin). Diagnosis of superimposed preeclampsia can be difficult in kidney transplant patients due to higher frequency of preexisting hypertension and proteinuria.”

Minor:

9. The images are of a very low quality

We have improved the quality and resolution of the images. However, on uploading the images, the resolution seems to be reduced in the pdf created. We have emailed the images as individual attachments so that it can be rectified.

10. The tables should follow a conventional order based upon publication date

We have revised the table as suggested based on the publication date.

Monica Limardo (Reviewer 2): The metanalysis is very interesting.

1. Authors identified studies all around the world from 1947 through 2017 and compared pregnancy outcomes to those of the most recent (2013-2016) US general population.

The main limitation of this study is that data were collected during several decades, during which kidney transplantation and obstetric care underwent great evolution. So, in the metanalysis it would be of paramount importance to consider also years of data collection.

Thank you for this valuable suggestion.

As mentioned by the reviewers, the better study design would be to look at data in the recent decade. Although we searched for studies from various data search engines from their date of
inception through 2017, published studies that were found to be eligible were from 1980-2017, and were included. The year of publication of the study is not correlated with the year in which they received kidney transplants. For example, majority of studies published after 2000 have study population that spans prior to 2000.

As suggested by reviewers, we performed a subgroup analysis of published studies 2000-2017. The results of the subgroup analysis were consistent with the study results. We would like to clarify that majority of published studies after 2000 had patients before 2000 included in their study population. Due to overlapping decades in the various studies, the results of the sub analysis have to be interpreted keeping this limitation in mind. We have added the subgroup analysis in the supplement.

It is expected for the outcomes to change due to improvement in obstetric care in kidney transplant recipients over the course of time. However, due to the above mentioned limitations of the various studies, where it is not possible to separate the pregnancies in kidney transplant recipients by decades, this remains the weakness of the study. We have added this in the limitation section.

2. Another limitation that should be underlined in the Discussion it that this is an unadjusted international meta-analysis that does not account for differences in socioeconomics and healthcare conditions among the different geographic regions

Thank you for bringing this important point. We have added this in the limitation on page 17.

Other comments:

3. Abstract: the time period from 1947 through 2017 should be reported in abstract methods

We have mentioned the time period in the abstract methods.

“We searched PubMed/MEDLINE, Elsevier EMBASE, Scopus, BIOSIS Previews, ISI Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials from date of inception through August 2017 for studies reporting pregnancy with kidney transplant.”

4. Abstract, conclusion: please report that this metaanalysis shows favourable live birth outcomes, as you reported in the conclusion of the paper

We have made the suggested change.
5. Pregnancy outcomes, line 38, "abortion": please precise if spontaneous abortion or therapeutic abortion or both

It was an induced or a therapeutic abortion. We have made the suggested change to induced abortion.

6. Discussion, page 12, line 38 "with national data": please precise "US recent national data"

We have changed it to “the US recent national data”.

7. Discussion: the finding that live birth rates were higher as compared to the recent US general population is similar to data reported from another recent metanalysis. However, this finding should be better discussed. It could be due to selection and/or reporting biases?

We have added this important point in the discussion.

“The higher live birth rate, although appears encouraging, may reflect a reporting bias or a selection bias in which relatively healthy women decided to pursue pregnancy, and subsequently received better medical support by multiple specialties. It is also important to consider that there are inconsistencies in definition of live birth rate used in various studies, for example live birth rate was defined as per 1,000 female transplant recipients in some studies, whereas per 1,000 pregnancies in transplant recipients in others.”

8. Discussion, page 14, line 16 -31, "although various…counselling" this part could be deleted, it seems not necessary to the discussion of results.

We have deleted this part.

9. Discussion, page 14, line 57-59 "however it is not recommended to stop steroid… of pregnancy." Please remove this sentence since it is not necessary to the discussion of results

We have removed this sentence from the discussion.

10. Discussion, page 16, line 35, "due to limitation of the study design": please make clear which are the limitations
We have specified the limitations of the study design.

“Overall, fetal outcomes in < 2 year interval seem most favorable in our study but merits further investigation due to limitation of the retrospective study design, small numbers, and possible reporting bias associated with data from voluntary registries.”

11. Conclusion, page 17, lines 16: please precise that data are from different decades

We have made the suggested change and added that data are from different decades.

“This meta analysis of pregnancy outcomes in 6712 pregnancies in 4174 kidney transplant recipients with data spread over different decades from all over the world shows favorable outcomes with live birth rates exceeding that in the recent national population.”

12. Conclusion, page 17, line 19: please precise "exceeding that in recent national population"

We have made the suggested change to “exceeding that in the recent national population.”

“This meta analysis of pregnancy outcomes in 6712 pregnancies in 4174 kidney transplant recipients with data from different decades from all over the world shows favorable outcomes with live birth rates exceeding that in the recent national population.”