Peer Review File

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Reviewer Comments

Reviewer A

The management of diabetic retinopathy (DR) in pregnancy is an important issue, particularly given the projected increase incidence and prevalence of both Type 1 and especially Type 2 diabetes in people of child bearing age worldwide.

Here, Mir and Finn present a review of the literature on this subject. Whilst their handling of the epidemiology in this field has been done well, attention to the following points may be helpful:

Comment 1. The multimodal imaging section has been written almost entirely without substantiation from any of the available published literature. For instance, the use of OCT for diabetic macular oedema – surely the authors can insert a reference regarding its use in diagnosing/monitoring DME, and also contrast it against the prior clinical diagnosis of CSME?

Reply 1. The multimodal imaging section has been amended with references to the published literature regarding the use of fundus photography, OCT, and FA.

Please see lines 145-159 for these changes and the addition of the relevant references.

Comment 2. The discussion of FFA in this same section also needs to be handled with better clinical relevance. Essentially, the quoted studies have shown that the dye crosses the placenta and also into breast milk, so before even consenting such a patient, the authors should really be asking/advising the reader as to whether such an investigation is really needed – ie in which situations would the FFA be vital in dictating, or changing, any management decisions?

Reply 2. Lines 159-172: The section on FA has been revised per the reviewer's recommendation.

Comment 3. Again in the same section, there is a mention of OCTA – but there is no mention of its current limitations vs standard FFA (namely, field of view). A discussion of OCTA is warranted in this section, given its non invasive nature, but the authors simply give a completely unsupported declaration that it is a "valuable alternative imaging modality". Based on what? There are several studies now using OCTA in non pregnant people with diabetes – what did they show that would be useful in the pregnant subject?

Reply 3. Line 178-188: We have incorporated reviewer's suggestions and revised the section on OCTA

Comment 4. The entire section on "Observation" has been written without any supportive references. How sure are the authors that patients with mild-moderate NPDR and DME will definitely improve and not worsen throughout pregnancy? Where is the literature that supports such a bold statement?

Reply 4. Line 202-214: Thank you for the suggestion, we recognize that some patient will have disease progression in which case they should be treated appropriately on a case-by-case basis. We have revised the observation section and included additional references per the reviewer's suggestion.

Comment 5. For all of the interventional treatments that have been discussed for DME in this review, there is no reference or recommendation as to when such treatments should be considered with respect to vision, or severity on imaging (eg macular thickness, or even early signs of poor prognosis such as DRIL, etc). The purpose of a review article is to summarise the current literature, and editorialise/give some guidance to the reader, based upon the available literature. This is severely lacking in these and all of the following sections in this review
Reply 5. At present there are no clinical trials or prospective studies that lay down definitive treatment algorithms for DME in pregnant patients. We thank the reviewer for the suggestion and in lines 217-229 we have added details about treatment in DME in non-pregnant patients. In pregnancy the visual and anatomical thresholds for treatment should be established on a case-by-case basis, depending on several patient factors, including but not limited to disease severity, gestational age, fellow eye status and patient's functional status.
Additional details have been added to each treatment section.

Comment 6. It should be noted that "Category C" is an outmoded designation by the FDA – these criteria have recently been substantially overhauled to be more clinically relevant –
see: https://www.fda.gov/vaccines-blood-biologics/biologics-rules/pregnancy-and-lactation-labeling-final-rule<
Reply 6. Lines 247 and 261: This statement has been removed from the manuscript

Comment 7. Reference to the findings of the Pittsburgh study in relation to the regression of DR changes after pregnancy need to be tempered by more recent studies that have had opposing results. Otherwise, the reader may assume that the DR changes seen during pregnancy will always regress after delivery, and this is often not the case
As stated above, the purpose of a review article is to summarise the current literature, and editorialise/give some guidance to the reader, based upon the available literature. This is severely lacking in many later sections of the review and the authors are encouraged to interrogate the available literature more thoroughly to produce substantiated recommendations, or at least an acknowledgement that there are significant gaps in the literature in some aspects that require further research before firm recommendations can be made.
Reply 7. Thank you to the reviewer for the suggestion. We have added guidelines, where available based on the current literature, including the addition of new references and acknowledging where evidence may be lacking in the treatment section and where treatment must be individualized.

Please see lines 257-261, 295-298, Lines 351-365

Reviewer B

Comment 1. Overall this is a very good summary of diabetic retinopathy in pregnancy and I congratulate the authors on this valuable contribution to the literature. My comments are below.

On page 4 lines 83-85, do the authors intend to state that the development of a new diagnosis of diabetic retinopathy during pregnancy is higher in type 1 than type 2 diabetes? If so this should be clarified.

Reply 1. Line 90: This has been clarified

Comment 2. On page 5 line 107 please define "NICE".

Reply 2. Line 118: Suggested change has been made

Comment 3. On page 6 in "Role of Multimodal Imaging" the authors mention OCTA as a valuable alternative imaging modality to fluorescein angiography in pregnant and nursing women. Are there any studies that support this statement?

Reply 3. Line 178-188: There are no studies specifically investigating the clinical use of OCTA in pregnant females with diabetes; evidence can be extrapolated from studies conducted in non-pregnant diabetic individuals. As OCTA is a relatively non-invasive and safe imaging modality for pregnant patients, it can be considered as an alternative to FA in certain clinical situations. The OCTA section has been revised to include relevant references.

Comment 4. On page 7 in "Observation", is there a reference to support that close observation, optimal blood glucose control, and blood pressure control can result in significant disease stabilization and resolution of diabetic macular edema?

Reply 4. Line 203-214: We have referenced additional studies and revised the observation section.

Comment 5. On page 7 in "focal laser", the authors state that focal laser remains the "first line" treatment for macular edema in pregnancy and this is supported by referencing an opinion piece in Retinal Physician. An opinion piece is not enough evidence to conclude that focal laser is first line. It may be appropriate to state that for many retina specialists, it is the treatment of choice.

Reply 5. Line 231: The text has been modified per the reviewer's recommendation

Comment 6. Please define Category C by the United States FDA when first mentioned in the manuscript on page 8.

Reply 6. This statement has been excluded based on Reviewer A's suggestion, please see above.

Comment 7. Page 8 line 167 states that treatment with anti-VEGF therapy in pregnancy is not desirable. What is the evidence, if any, that supports this statement?

Reply 7. We have clarified this statement on anti-VEGF in lines 257-261.

Comment 8. What is the evidence supporting waiting 3 months after anti-VEGF injection prior to conceiving (page 9 line 192)?

Reply 8. There are no studies to establish a standard duration of a safe "anti-VEGF free period" prior to conception. The 3-month recommendation is to allow enough time for the drug to be eliminated from the mothers systemic circulation (duration usually equivalent to ~5-6 drug half lives)

Comment 9. Page 9 lines 196-198 state anti-VEGF agents should only be administered in pregnant women if "absolutely necessary and other treatment modalities have failed." This is a strong statement to make. Is there evidence supporting this? Perhaps it would be more appropriate, and softer, to state that retina specialists may consider other treatment modalities prior to considering anti-VEGF for DME in pregnancy given the paucity of information available on safety of anti-VEGF in pregnancy? The manuscript doesn't provide strong evidence that anti-VEGF injections are harmful in pregnancy; rather, it makes the case that their safety has not been well studied.

Reply 9. Thank you for the suggestion. Line 295-298: This statement has been revised

Comment 10. Please describe why local anesthesia is preferable to general anesthesia in pregnancy.

Reply 10. Line 335-338: General anesthesia is associated with increased maternal (DVT, pulmonary embolism, aspiration) and fetal complications (spontaneous abortion and pre-term labor).

Anesthesia, Editor(s): Shahrokh C. Bagheri, Chris Jo, Clinical Review of Oral and Maxillofacial Surgery, Mosby, 2008, Pages 45-63, ISBN 9780323045742

Comment 11. Using the words "transient" and "persistent" is somewhat contradictory when describing the effects of pregnancy on page 11 lines 240-241; I suggest simply stating that the effects are transient and resolve 6-12 months after delivery.

Reply 11. Line 354: The suggested revision has been made

Comment 12. The last sentence before the conclusion does not need its own paragraph. It can be added to the paragraph prior.

Reply 12. This edit has been made in Line 365, thank you

Comment 13. In the conclusion, it may be worth stating that if anti-VEGF intravitreal injection is considered during pregnancy, consideration should be given to ranibizumab over bevacizumab given its shorter half-life and faster plasma clearance.

Reply 13. Line 398-99: This has been included in the conclusion section