Author’s response to reviews

Title: Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): is it clinically useful?

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Author’s response to reviews:

James Mockridge
Editor
BMC Endocrine Disorders

Dear Editor,

Please find enclosed our revised manuscript entitled "Presence of diabetes-specific autoimmunity in women with Gestational Diabetes Mellitus (GDM) predicts impaired glucose regulation at follow-up" (BEND-D-18-00103R1), that we are submitting as an article for “Debate” to BMC Endocrine Disorders.

We believe that we have answered to all the referee’s suggestions, and changed the manuscript accordingly. All changes have been highlighted in the manuscript by red text. In our point-by-point answer to the reviewers we have explained in details all the changes that were made in the manuscript.

In particular, as recommended, we explained and discussed the reasons, in our opinion, not to test all GDM women for the presence of T1D autoantibodies, but only when the clustering of clinical parameters were strongly suggestive of an autoimmune form of GDM. Also, we corrected the Practice Points, as suggested by the reviewers. Finally, we revised the English language.
We believe that this topic of autoimmunity in gestational diabetes is worth being discussed and of interest for BMC Endocrine Disorders, and we thank you again for the opportunity to be considered for publication in BMC Endocrine Disorders.

With best regard

Marco G. Baroni MD, PhD
Associate Professor of Endocrinology

Point-by-point answers to the referees

Reviewer n. 1

Minor English wording changes/editing needed throughout.

We have reviewed the manuscript for English wording/editing, as suggested

Overall this narrative review covers the relevant issues and the conclusion reflects that from published data.

There was no mention regarding the occasional presentation of T1D acutely in pregnancy with for example DKA. Although this is beyond the specific topic of this paper I would like to see1 sentence on this in the introduction section.

We thank the reviewer for her comments. We have added a sentence regarding the occurrence of DKA as a first presentation of GDM in the introduction, at page 3 par. 1 lines 6-11.

Reviewer n.2
First of all, we wish to thank this reviewer for her comments, which are extremely appropriate and helpful. There are some arguments were there might not be full agreement, but we want to point out that we thoughtfully discussed some opinions that may not receive full support, and this is one of the reasons we decided to write this manuscript for debate.

With regards to the specific comments:

Major comments

1. This seems to be a revised version of the manuscript. Has the manuscript been reviewed earlier? I have not seen it before and have no information about the previous comments.

No, this manuscript has not been reviewed earlier; there were some editorial changes that were requested by the editorial office at the time of the first submission, and this is why the manuscript reference is -R1

2. Autoantibodies against beta cells during GDM could be a predictor for later development of T1D. The conclusion from this manuscript is that autoantibodies should not be tested during pregnancy. It should be better to test for autoantibodies a time after delivery. One reason for this is that the immune system is suppressed during pregnancy. This will, however only lead to false negative cases and not false positive cases. A second reason is that testing would stress the women and the psychological effects should be a reason for not testing for autoantibodies (page 6, line 10-11 from bottom). This is not in agreement with good clinical practice. Presence of autoantibodies is a strong predictor (50-96%) for later development of T1D. If T1D develop soon after delivery, before the follow up visit, these cases would be missed. Many women do not show up for follow up visit and these would also be missed.

The reviewer raises important points. In our opinion, autoantibodies should not be tested during pregnancy in all GDM women. This because in several studies, including ours, the prevalence of T1D autoantibodies is low, and similar between pregnant women with and without GDM.

Indeed a comparable prevalence between women with and without GDM has been observed in numerous large studies (for example in Dozio N et al. Low prevalence of islet autoantibodies in patients with gestational diabetes mellitus. Diabetes Care 1997;1: 81-83; Weng J, et al. (2002) Screening for MODY mutations, GAD antibodies, and type 1 diabetes associated HLA genotypes in women with gestational diabetes mellitus. Diabetes Care 25(1):68e71; Petersen JS, et al. GAD65 autoantibodies in women with gestational or insulin dependent diabetes mellitus

Also, as the reviewer recognizes, there is a chance to have false negative cases, which would be dismissed as cases of non-autoimmune GDM (point added at page 8 lines 2-3). Thus it is advisable, in our opinion, to wait after pregnancy.

Finally, follow-up studies have show that overt diabetes appears usually from the first year after delivery onward. In the study from Nilsson et al (Clinical use of C-peptide and β-cells specific autoantibodies during gestational diabetes mellitus, Pract Diab 2012), for example, less than 20% of AABs+ve GDM women developed T1D within 1 year after pregnancy, with the vast majority developing T1D later. Thus, it is extremely important to ensure that follow-up evaluation (within 6-12 weeks, as by current guidelines) is performed in all GDM women after pregnancy, assessing AABs if indicated by the clinical situation. This point has been discussed at page 8 par.3

With regards to psychological effects as a reason for delaying autoantibodies testing, we discussed this point in consideration to the fact that GDM have similar clinical outcomes regardless of the presence of AABs. Thus, given that a GDM pregnancy per se is a time of emotional distress (Judith Parsons, Katherine Sparrow, Khalida Ismail, Katharine Hunt, Helen Rogers and Angus Forbes. Experiences of gestational diabetes and gestational diabetes care: a focus group and interview study BMC Pregnancy Childbirth. 2018 Jan 11;18(1):25.), a universal autoimmune screening may expose women to unjustified stress at this particular time. This point has been clarified at page 6 last par and page 7 par 1.

3. This manuscript has a lot of contradictions. It is unclear if the authors mean that there are, or are not, clinical features for women with autoantibodies. On page 8 line 4-5 specific clinical features are mentioned and on page 9 line 4-5 several clinical features are described but in the conclusion on page 8 line 2-3 from bottom it is stated that "specific clinical features predicting… have not been established”.

We apologize for not making this point clear. At page 8 we are discussing the reasons to test for autoantibodies after delivery, mentioning possible clinical feature suggestive of T1D after delivery that should lead to testing, like persistent hyperglycaemia without features of insulin-resistance.
Earlier (in the section “is it useful to test during pregnancy?”) we discussed that there isn’t a unanimous consensus on which clinical features predict antibody positivity in GDM during pregnancy.

Obviously, as we mention in our conclusions, if a cluster of clinical features (young age, low BMI, early insulin therapy, presence of ketones) strongly suggestive of a T1D-like form of GDM is present, testing for autoantibodies during pregnancy is indicated.

This point has been added in the section “is it useful to test during pregnancy?” at page 7 par. 3 lines 9-13, and in the conclusions at page 9 last paragraph.

4. In the conclusion section page 8, line 3, it is stated that GADA is not more frequent in women with GDM compared to pregnant women without GDM. This is not true. The authors themselves refer to several publications reporting higher frequency of GADA among women with GDM than without GDM.

GADA are indeed the most common autoantibody compared to the other AABs. With regards to the frequency of all AABs in women with and without GDM, several papers, including our, failed to find significant differences. As discussed in our answer to point n. 2, a similar prevalence between women with and without GDM has been observed in numerous large studies (refs are listed above and are cited in the manuscript) (19,33-35,43,44). As we discuss at page 6 (last par.) and page 7 par. 1, aside from acute forms of presentations, there is not a strong correlation between autoantibody positivity and beta-cell impairment.

5. In the Practice points on page 9 there are some sentences that are not correct.

2. Statement no 2 ”there is no difference between women with GDM depending on if GADA are present or not. See comments above.

We refer to the fact that the discovery of AABs (all AAbs not only GADA) in GDM women is usually not associated to significant difference in clinical outcomes (as discussed at page 6-7 and in the conclusions at page 9 par. 2) and treatments (refs 22,41,43,53,63 at page 7).

2. Practice points number four: GDM can per definition not continue after delivery.
The reviewer is correct, we inappropriately stated that remission of GDM is common, but we intended hyperglycaemia. We apologize for this, and the phrase has been changed.

3. Practice points number 5. Antibody positive women keep antibody positivity and they have an increased risk for T1D. Most of them have a normal glucose tolerance directly after delivery.

We may have not been clear in this point, which was referred to one of the reasons to test for AAbs after delivery, that is persistence of hyperglycaemia. We have changed the phrase indicating that: “Most women have normal glucose tolerance after delivery; if impaired glucose regulation persists, autoantibody screening is recommended.”

Minor comment

In the abstract it is stated that autoantibodies are detected in a small percentage >10% which means ”more than 10%”. It should be <10%. Which means ”less than”. Despite of this, there is on page 4 listed a lot of publications describing higher frequency of autoantibodies than 10%.

The referee is correct; the frequency is less than 10%. We apologize for the mistake in the abstract, and we have corrected the sentence in the abstract.

ACADEMIC PEER REVIEWER

ADDITIONAL REQUESTS/SUGGESTIONS:

The practice points in a box at the end of the article should be referenced in the text somewhere or is it just highlights/summary findings of the article/debate?

In our view it highlights and summarizes the findings in the article. However, we could make reference to it in the conclusions, and we have added it at page 9 last par.