Author’s response to reviews

Title: Risk factors associated with the development of postpartum diabetes in Japanese women with gestational diabetes

Authors:

Yukari Kugishima (zakky390@yahoo.co.jp)
Ichiro Yasuhi (yasuhi@nagasaki-mc.com)
Hiroshi Yamashita (hyamashita@nagasaki-mc.com)
So Sugimi (sugimis@nagasaki-mc.com)
Yasushi Umezaki (umezaki@nagasaki-mc.com)
Sachie Suga (ssuga@nagasaki-mc.com)
Masashi Fukuda (masashi.fukuda@nagasaki-mc.com)
Nobuko Kusuda (kusuda@nagasaki-mc.com)

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RESPONSE TO REVIEWERS

Kerstin Berntorp (Reviewer 1):

The aim of this retrospective study was to identify risk factors associated with the development of postpartum diabetes in Japanese women with a history of gestational diabetes mellitus over a longer postpartum period than previously reported by the same group (6-8 weeks) and to evaluate whether the risk of postpartum diabetes differ between women diagnosed by the previous Japanese GDM criteria and those proposed by the IADPSG.

1. Several risk factors for postpartum diabetes have been identified in a number of studies over the years based on different populations and diagnostic criteria, such as fasting or 2-h plasma glucose level during the diagnostic OGTT during pregnancy, as well as more recently pregnancy HbA1c. However, how the new IADPSG criteria will affect the postpartum diabetes risk is yet not known and therefore the most interesting part of this study. Unfortunately, the present material is still too small and the follow-up time too short
to adequately address this question. It would have been desirable if the two groups of women (diagnosed according to the previous criteria and the new ones) had been evaluated as two separate groups, especially since there was a significant difference in follow-up time (old criteria GDM during an 8-year period 2003-2010, mean follow-up period 83 weeks, and new criteria GDM during a 5-year period 2010-2014, mean 59 weeks, p = 0.0006) which can explain the non-significant difference in diabetes frequency between the old criteria (9.6%) and new criteria (11.2%). Therefore, all results throughout the study should be adjusted for the difference in follow-up time. Furthermore, glucose levels and HbA1c levels should also be given in SI units (mmol/L and mmol/mol, respectively) throughout, since many readers are not familiar with the mg and % values given. Many countries in Europe have changed to the IFCC-agreement on reporting HbA1c in mmol/mol. For further comments see below.

Response: As the reviewer mentioned, although the follow-up (f/u) period differed between the different criteria, it did not differ between the women who developed diabetes and those who did not (Table 3). The f/u period was not associated with the development of diabetes, either (we added the data of univariate analysis in Table 4). In addition, regarding the association between the diagnostic criteria and the development of diabetes, we examined the effect of the f/u period on the results of the univariate analysis and found that the association remained non-significant after adjusting for the f/u period. We have now added these findings to Table 4. We also examined the effects of the f/u period on the multivariate analysis results in Table 5 and 6 and found that the results were unchanged after adding the f/u period as a confounding variable in Model 2. Consequently, we concluded that the difference in the follow-up periods between the different diagnostic criteria did not affect the conclusion in this study.

In addition, because the proportion of women who had at least two f/u test and those who had a f/u period exceeding 12 months did not differ between the different criteria groups (Table 2), we do not think the quality of the follow-up study differed between the different criteria groups. Given these results, we believe that the difference in the f/u period between the groups did not markedly influence the conclusion in this study.

We have now mentioned the number of women who developed postpartum diabetes in Table 2 and added the following text to the Results section:

“Eleven (9.5%) and 21 (11.1%) women with diabetes were included in the JSOG and IADPSG groups, respectively (Table 2); the incidence was not different between the different diagnostic criteria group even after adjusting for the follow-up period.”

We also revised Table 5 and 6 to include the results of analyses in which the f/u period was added as a confounder.

Regarding the SI units, we usually use mg/dl and % for glucose and HbA1c values in Japan, as SI units are not familiar to Japanese readers. If it would be preferable for us to use SI unit as the
regular format in this Journal, we would like to include both units to help any Japanese readers more easily understand the values.

2. Pagination is missing throughout.

Response: We have now added page numbers.

Abstract

3. Background line 18: IADPSG stands for International Association…… not Society. The same refers to List of abbreviations.

Response: We apologize for this error and have now corrected it.

4. Results: The first section is unclear and hard to follow. How many women were primarily identified as GDM by the old and the new criteria, respectively, and how many of these had follow-up data in the respective group? Give follow-up data for both groups separately concerning follow-up time and the number of women diagnosed with diabetes in each group (11/116 (9.4%) old criteria and 21/190 (11.1%) new criteria. The results in the multivariate analysis should be adjusted for follow-up time.

Response: During the study period, 354 women were diagnosed with GDM, including 136 and 218 women diagnosed under the old and the new criteria, respectively. Among them, 116 (85.3%) and 190 (87.2%) women diagnosed under the old and the new criteria, respectively, had at least one postpartum OGTT. To clarify these results, we revised the first sentence in the Results of the Abstract as follows:

From:

“Among 354 women with GDM, 306 women (86%) underwent at least one follow-up OGTT.”

To:

“Among 354 women diagnosed with GDM during the study period, 306 (86%) (116/136 [85.3%] and 190/218 [87.2%] under the previous criteria and the IADPSG criteria, respectively) who underwent at least 1 follow-up OGTT were included in the study.”
Regarding the follow-up period between the criteria in women who developed postpartum diabetes, women diagnosed under the IADPSG criteria had a significantly shorter duration of follow-up than those diagnosed under the old criteria (see Table below). Accordingly, women diagnosed under the new criteria more rapidly developed diabetes after delivery. We have now mentioned this in the Results section as follows:

“Regarding the time period from the index delivery to the onset of diabetes in those who developed diabetes, women diagnosed under the IADPSG criteria developed diabetes significantly sooner than those diagnosed under the JSOG criteria (44±26 vs. 88±78 weeks, p=0.024).”

Table. The difference in the follow-up period between women who developed postpartum diabetes by the different criteria

<table>
<thead>
<tr>
<th></th>
<th>Old (JSOG) criteria</th>
<th>New (IADPSG) criteria</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women who developed diabetes</td>
<td>11 (9.5%)</td>
<td>21 (11.1%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Follow-up time (weeks)</td>
<td>88±78</td>
<td>44±26</td>
<td></td>
</tr>
</tbody>
</table>

Furthermore, we have added the following to the second paragraph in the Discussion section:

“In addition, in women diagnosed with postpartum diabetes, the duration from the index delivery to the development of diabetes was significantly shorter in the IADPSG group than in the JSOG group.”

We also revised the next sentence in the same paragraph as follows:

From:

“Thus, in comparison to the previous criteria, the IADPSG criteria seem to recognize more women who develop postpartum diabetes.”

To:

“Thus, in comparison to the previous criteria, the IADPSG criteria seemed to recognize more women who develop postpartum diabetes earlier.”

5. Give results in SI-units as well, see above.

Response: We have already addressed this above (Reply to comment 1).
6. Conclusion: Adjust according to results after taking the difference in follow-up time into account.

Response: As mentioned above, the results after adjusting for the follow-up time did not change the conclusion.

Methods

7. First paragraph line 42-46: … before June 2010 ……… after July 2010 … unclear. Should it be up to June 2010 and from July 2010? Table 1 gives OGTT thresholds only. Please also inform about the screening procedure. Did all women undergo a 75 g OGTT or are they screened by a 50 g test? Which pregnancy week? Did the screening procedure change when the IADPSG criteria were introduced?

Response: As suggested, we have now clarified this point as follows:

“We used two different diagnostic criteria during this period: the Japan Society of Obstetrics and Gynecology (JSOG) criteria [8], which were used until June 2010; and the IADPSG criteria, which were used from July 2010 (Table 1).”

We also revised the description in Table 1.

Regarding the screening method for GDM, we used the same method during both periods, which we have now clarified as follows:

“In both of the study periods with different diagnostic criteria, to screen for GDM during pregnancy, we performed universal screening of all pregnant women using a 50-g glucose challenge test around 24 weeks’ gestation; those with values of ≥135 mg/dL underwent a diagnostic 75-g oral glucose tolerance test (OGTT) after overnight fasting. We also measured the HbA1c values at the time of the diagnostic OGTT.”

8. Next page paragraph 3 line 53: (defined as unspecified diabetes within second-degree relatives) unclear, do you mean (defined as unspecified diabetes in first and second-degree relatives)?

Response: We apologize for the vague description. We have now revised this point as follows:

“…family history of diabetes (defined as unspecified diabetes among first- and second-degree relatives)…”
9. Next page last paragraph: Add information about the statistics used in Table 2 and 3.

Response: Regarding the statistical analyses, we added a description to the bottom of the Tables. We also added a sentence to the last paragraph in the Method section as follows:

“We also used Student’s t-test and a chi-squared test to compare numerical variables and the difference in ratios between groups, respectively.”

Results

10. First paragraph line 32-39. The information about PG levels during the diagnostic OGTT can be omitted since it could be understood from Table 1 that the PG levels by definition were higher in the JSOG group. It would be of interest to add information in Table 2 on the number of women in the respective group who had only one early follow-up visit (rather than at least two), since these women most likely had pregestational diabetes.

Response: Among those who only underwent 1 follow-up OGTT, we found 3 women with diabetes in each different criteria group (representing 9.1% in the JSOG group [n=33] and 7.1% in the IADPSG group [n=42]), a non-significant difference between the groups. The first follow-up OGTT was performed between 6 and 8 weeks postpartum in all six of these women. Therefore, these women “most likely had pregestational diabetes”. Again, there was no significant difference between the groups (p=0.76). However, more than 90% of women did not have diabetes at the one postpartum OGTT they underwent, in contrast to the reviewer’s suggestion. We therefore do not believe that this information has any significance.

11. Next page line 21: The word diabetic should be avoided, change diabetic women to women with diabetes.

Response: As suggested, we changed the phrase from “diabetic women” to “women with diabetes”.

12. Next paragraph: Only risk factors identified as significant (p < 0.05) in univariate analysis were included in the multivariate model. However, also those of known interest and of borderline significance could be included. Since fasting glucose levels have been identified as a risk factor in many studies it would have been of interest to also include fasting PG in the model as well, and if non-significant this could be discussed further, see below.
Response: Regarding the borderline-significant variables of fasting PG (p=0.091) and 1-h PG (p=0.056), we already performed an analysis with the fasting PG as a confounder in the multivariate analysis (Model 2 in Tables 5 & 6) and found that the fasting PG was not significant and did not affect the results in the multivariate analysis. As suggested, we added both of these borderline-significant variables as confounders to Model 2 and confirmed our findings as follows in the Results section:

“Because fasting and the 1-h PG showed near-significance in the univariate analysis (Table 4), we also examined the association between those two variables and the development of diabetes by a multivariate analysis including these two variables in addition to the four significant variables and found that neither fasting nor the 1-h PG was significantly associated with the postpartum disorder.”

Tables

13. Add information under all tables about the statistical method used.

Response: We have now added the following description to the bottom of the Table:

“P values represent comparisons between the JSOG and IADPSG criteria using Student’s t-test or a chi-squared test.”

14. In Table 2, what does Rx in Insulin Rx stand for? Explain and add to abbreviation list.

Response: We changed “insulin Rx” to “insulin therapy” in Tables 2 to 6.

15. Table 4 could be replaced by mentioning the results in the text.

Response: We believe that Table 4 provides some useful information for assessing the significance of the association between each variable and the postpartum development of diabetes, especially when considering near-significant or far-significant variables.

16. Adjust for follow-up period in the logistic regression analysis in Table 5 and 6. Model 1 could be excluded from these tables since the adjusted values are those of interest.

Response: We feel it may be informative to provide both the model including the minimum number of variables with possible significance (like Model 1) and the model including as many confounders as considerable (like Model 2), although the results did not differ markedly between
the models. Rather, the fact that the results were very similar between the two models is important, as this indicates that the association between those two significant predictors and the postpartum development of diabetes was not markedly influenced by the confounders.

Discussion

17. Modify the aims of the study (Introduction) and the following discussion according to the remarks above. Address further the limitations of the study, which was unpowered to show a difference in postpartum diabetes comparing the old and new criteria, and the effect of these criteria on the risk factors for postpartum diabetes.

Response: As we mentioned in the reply to the reviewer’s introduction, the major issue mentioned in this comment was the difference in the follow-up period. We have already addressed this issue.

Regarding the small sample size, we agree with the comment and have now added the following description to the Discussion:

“Because of the small sample size in this study, we were unable to conclude that other variables, including prepregnancy obesity and insulin therapy during pregnancy as well as fasting PG during the diagnostic OGTT for GDM, were not significant predictors for the development of postpartum diabetes. Because of the small sample size, we were unable to perform analyses limited to women were diagnosed under the IADPSG criteria. Although our results suggest that the IADPSG criteria are efficient at identifying women with GDM at risk of developing postpartum diabetes, further prospective cohort studies with a larger sample size are necessary to draw conclusions on this issue.”

18. Second page line 28-32: Correct prevalence 11/116 (9.4%) old criteria and 21/190 (11.1%) new criteria instead of 9.6% and 11.2%, respectively?

Response: We apologize for this careless mistake and have now corrected it.

19. Next page line 3-11: The difference in follow-up time between the JSOG group and IADPSG group is mentioned to explain the difference between the present results and those found by others, i.e. that the IADPSG criteria seem to better recognize women at risk for postpartum diabetes. Why not adjust for this difference in follow-up time?

Response: We have already addressed this issue.
20. Same page line 21-35 makes no sense. The IADPSG criteria are based on the risk of adverse neonatal outcomes (LGA etc.) and not on the risk of developing postpartum diabetes.

Response: This is correct, as we mentioned in the Background section. We have revised the section as follows:

“Because the number of women who were diagnosed in the IADPSG group was higher than that in the CC group, the IADPSG criteria could be superior for identifying women with postpartum glucose disorder who would have been missed by the CC criteria [10], even though the IADPSG criteria are based on only the perinatal outcomes and not on the risk of developing postpartum diabetes.”

21. Same page line 46-49: … the follow-up tests after delivery have been suboptimal [ ] in spite of the current recommendations [ ]. Please comment on which recommendations.

Response: As suggested, we have added the following text:

“There is already evidence to show that women with a history of GDM are at significant risk for the development of type 2 diabetes; however, the follow-up tests after delivery have been suboptimal [11,12], in spite of the current recommendations including early postpartum diabetic screening at 6-12 weeks postpartum and further follow-up tests [13-15].”

22. The study of M. Ekelund and al. is referred to (reference 20). There have been quite a few studies addressing HbA1c as a predictor of postpartum diabetes after this, listed below, which should be referred to.


Response: As suggested, we have now added some sentences to the Discussion as follows:

“Several studies addressed HbA1c as a parameter for predicting postpartum diabetes in women with GDM among different races and ethnicities with different diagnostic criteria for GDM and
follow-up duration [Claesson; H. Liu; S.S. Kwon; V. Bartakova]. Those studies found significant independent predictive cut-off values for the development of diabetes between 5.4% and 5.7%. Again, a modestly elevated level HbA1c seems to be a significant predictor regardless of race and ethnicity.”

We have also added the four references listed by the reviewer.

23. Bottom 5:tn page of Discussion: We did not find a significant association between fasting PG and diabetes; ...... referring to M. Ekelund et al. However, the fasting PG was not included in the present multivariate model (see above), which could have been of interest. If not identified as a predictor of postpartum diabetes it could be explained by ethnicity, as fasting PG has been reported to be less sensitive to for the diagnosis of diabetes than the 2-h PG level in the Asian population (Hsu et al. Diabetes Care 2012;3:1189-1198.)

Response: As mentioned above, in the multivariate analysis model including the fasting PG, we did not this parameter to be a significant predictor. According to the reviewer’s suggestion, we referenced the study by Hsu in the Discussion.

Sara Meltzer (Reviewer 2):

The authors retrospectively assessed the risk and indicating risk factors in pregnancy for postpartum (PP) DM over the period from 2003 -2014. There was 304/354(86%) women who came for PP Testing. They indicate that those factors shown to be predictive in a recent meta-analysis apply to their population and provide risk ratios for important values for a Japanese population which may be very helpful, as there appear to be nuances of various ethnic risks.

1. It is very difficult to understand what the previous Japanese GDM diagnostic values were. The referenced journal - Acta Obstet Gynaecol Jpn 1984; 36: 2055- is not easy to access to help the reader to understand. It is not stated clearly if there was and still is universal screening of pregnant women or based on risk factors as in parts of Europe. Wasn't the glucose load 100g in Japan prior to the use of the IADPSG values? This easily explains the higher values on the pregnancy OGTT. To permit comparatives, I would suggest the authors indicate if screening was universal, at what time in the pregnancy, whether a glucose challenge test of 50 g was ever used or not and the number of grams of glucose in the standardized glucose load prior to the use of the IADPSG/WHO 2013 Hyperglycemia in pregnancy values.

Response: We have already addressed this above (Reply to comment 7 of Reviewer #1).
2. What is the results using the 1 hour value - if it is equivalent to the 2 h value, maybe one day the glucose assessment for pregnancy could be fasting & 1 h? Saving time & money for pregnant women & the health systems. Was there a cutoff value for the 1h? In Japanese women, if the 2 h antepartum value is the highest risk, this may be important for future recommendations in Japan.

Response: The 1-h value showed near-significance in the univariate analysis but was not significant in the multivariate analysis. We have already addressed this issue in our reply to comment 12 of Reviewer #1.

3. In Table 3, could they show more columns to allow comparisons of former Japanese diagnostic criteria vs IADPSG group for diabetes /no DM post partum to see if they appear different - at least for the reader to see the raw data? Leave the first 2 columns with p values as is and add additional columns to the right for the other groups Jap values with or without GDM PP + IADPSG tested women with or without DM PP.

Response: As we mentioned in our reply to Reviewer 1, the difference in the diagnostic criteria did not significantly affect the postpartum development of diabetes. In addition, the small sample size in the subgroups analysis weakened the statistical power, so we believe that a subgroup analysis would provide misleading results.

4. In the table 5&6 looking at comparative RR for PP DM & for predictability of DM, if the 1 h value was used, was the risk ratio done and non-significant? In fact, it would be excellent to include the fasting as well. It appears as if Asian populations have more risk indicated by post load - including all 3 OGTT values would underline this issue.

Response: We have already addressed this above (Reply to comment 12 of Reviewer #1).

5. Overall, I think that this paper is well written and does provide useful information for a large & specific Japanese population.

Response: We greatly appreciate your comment.
Teri Hernandez (Reviewer 3):

Overall Comments:

The authors have identified risk factors for the development of Type 2 diabetes postpartum within Japanese women with a history of GDM. Importantly, they sought to identify if there was a greater incidence of postpartum Type 2 diabetes among women diagnosed with GDM by the former Japanese criteria vs. the contemporary IADPSG criteria. The primary risk factors identified (A1c and 2-hour post 75g glucose challenge plasma glucose, both from the day of antepartum GDM diagnosis) are not new. Moreover, the lack of difference in postpartum Type 2 diabetes rate between diagnostic criteria could be due to lack of statistical power. Finally, the authors did not acknowledge the fact that the IADPSG criteria were not meant to identify women at high risk for postpartum diabetes, as with the Carpenter and Coustan criteria. Instead, the IADPSG criteria glucose thresholds were chosen to identify a 1.75-fold increased risk of offspring LGA (see Ryan EA, Diabetologia, 2011, 54:480-486). This is a very important point of discussion that can be used to provide context for interpreting these data.

Response: The reviewer pointed out a very important issue in this study. We have now added a comment on this point to the limitations section in the Discussion, as we replied to comment 20 of Reviewer #1.

Other comments:

Abstract

1. First sentence: is a fragment. The second sentence is unclear

Response: We apologize for the confusion and have revised this sentence now.

2. Methods: Please make it clear that the outcome is postpartum Type 2 diabetes—not to be confused with Type 1 diabetes (also increasing in incidence after pregnancy)

Response: A growing proportion of the Japanese population is developing type 2 diabetes, and 95% of Japanese patients with diabetes have type 2 diabetes. We believe that the majority of the patients who developed diabetes during the postpartum period in our study had type 2 diabetes. However, we did not measure the anti-GAD antibody in all patients with diabetes in this study. In addition, it may be difficult to distinguish type 1 diabetes in some patients whose pancreatic islet cell damage progress very slowly (slowly progressive insulin-dependent diabetes [SPIDDM]) from type 2 diabetes. Accordingly, we cannot confirm that all of the patients who
developed postpartum diabetes in this study had type 2 diabetes. However, we believe that the majority had type 2 disease (likely more than 95%), meaning that less than 1 in 32 patients had type 1 diabetes in this study.

3. Results: Suggest making it clear that the 2-hr PG and A1c are both from the day of GDM diagnosis--otherwise readers might think these variables were collected after diagnosis.

Response: We have now clarified our point as follows:

“A multivariate logistic regression analysis revealed that HbA1c and 2-h plasma glucose (PG) at the time of the diagnostic OGTT during pregnancy were independent predictors of the development of diabetes after adjusting for confounders.”

4. The last sentence of the results: is not clear as written.

Response: We have now clarified our point as follows:

“The adjusted relative risk of HbA1c ≥5.6% for the development of diabetes was 4.84 (95% confidence interval, 1.59-17.23), while that of 2-h PG ≥183 mg/dl was 7.08 (2.68-19.53).”

Introduction

1. As described above, it is strongly suggested that the authors describe that the IADPSG criteria glucose thresholds are based on offspring risk for LGA. Also, throughout the manuscript, make it clear that postpartum Type 2 diabetes is the phenotype of interest.

Response: We have already addressed this issue.

Methods

1. Why was 2003 chosen for the early end of the data abstraction years? Was GDM screening standard of care/universal in 2003? Please clarify. The ACHOIS trial was published in 2005 and provided the first evidence from a RCT that diagnosis and management of GDM improves perinatal outcomes--before that trial was published, universal screening may not have been instituted and this could be a confounding variable in terms of the incidence of GDM.
Response: In April 2002, we first introduced the universal screening and diagnostic system for detecting GDM as well as postpartum follow-up in our hospital; this system was then established later the same year. Therefore, we chose January 2003 as the starting point of the study period.

2. Maternal characteristics: Were history of macrosomia/LGA and parity included? Were women with twin gestations excluded?

Response: We included women with a history of macrosomia/LGA. In those women, we regularly checked their HbA1c and fasting PG or performed a 75-g OGTT at their first visit in the index pregnancy and confirmed that they did not have diabetes in the first trimester. If they had overt diabetes during pregnancy, we excluded them from the study, as we mentioned in the Method section. We also included five twin pregnancies. As we addressed only the maternal characteristics and not the perinatal outcomes, we do not believe this affected the results of this study.

3. Power: Although this is a retrospective study, the authors did not make the primary outcome clear. It is still possible to estimate power in order to have a metric for the minimum number of cases needed to be archived in order to answer the question. Because there was no power analysis or any mention at all that this was considered, it is possible that the lack of difference in type 2 diabetes incidence between the older vs. newer criteria could be a Type 2 error--it is recommended that the authors acknowledge this for readers.

Response: Because this is a retrospective cohort study, we did not perform a power analysis. As with most such retrospective studies, we do not believe a power analysis was necessary. However, we have now mentioned the small sample size as a limitation of this study in the Discussion.

4. Statistics: The ROC curves are not described in the statistics section. Moreover, the difference in the analyses between Tables 5 vs. 6 are not described, nor are they clear.

Response: We have now added the following sentence to the Methods section:

“In the multivariate analysis, we converted the factors that were numerically associated with the development of postpartum diabetes into categorical variables as a clinical viewpoint. A receiver operator characteristic (ROC) curve was used to identify the optimum cut-off values for those variables.”
Discussion

1. Second paragraph, last sentence: It is strongly recommended that this statement be removed--it is not a valid speculation. The Carpenter & Coustan criteria glucose thresholds were validated and chosen based on maternal risk for postpartum diabetes--the IADPSG criteria were not.

Response: We have already addressed this above (Reply to comment 20 of Reviewer #1).

2. Paragraph beginning with "In our previous study…". It is recommended that this paragraph be removed as it is not relevant to this study.

Response: The disturbance of early-phase insulin secretion is a significant characteristic as an early phase of the development of type 2 diabetes in Japanese population. The studies listed below in Japanese population have reported that worsening from normal glucose tolerance to IGT in Japanese subjects is associated with decreased early-phase insulin secretion in non-obese as well as obese subjects and that impaired early-phase insulin secretion is the initial abnormality observed in the development of glucose intolerance in Japanese individuals. We think the paragraph is appropriate to discuss such Japanese characteristics in the Discussion section.

