Author’s response to reviews

Title: Prediction of fetal acidemia in placental abruption

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Version: 3 Date: 17 May 2013

Author's response to reviews: see over
May 17, 2013

Dear Editors:

Please find attached our revised manuscript entitled “Prediction of fetal acidemia in placental abruption” and a separate document detailing our responses to the reviewers’ comments.

Thank you for giving us the opportunity to resubmit the manuscript, which we revised according to the reviewers’ suggestions.

We hope that the revised manuscript is now suitable for publication.

Sincerely yours,

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Reviewer’s report (MB)

Major compulsory revisions

1) The study population includes 222 subjects, but it is not clear whether this study is powered to direct any significant potential predictor. This is particularly relevant as there are only 43 ‘cases’, which more than 30 variables assessed for their value as a predictor of fetal acidaemia. I assume there to be categories with small numbers (or zero), as suggested by the use of the Fisher’s exact test.

Answer: Thank you for your comment. Through this study, several predictive factors for fetal acidemia in placental abruption have been clarified. And, we wanted to show the potential usefulness of ‘severe abruption score’ established now. Therefore, this study is an exploratory study. We don’t think it is necessary to consider the ‘power’ and the case numbers for the ‘power’ analysis.

2) A clear list of all variables studied would be useful.

Answer: Thank you for your advice. A list of all variables studied has been added as ‘Table 1’ in the revised manuscript. Then, the numbers of tables have been changed afterward.

3) There is no mention of missing data, or how this was handled. It is not clear why chronic abruption were excluded.

Answer: We could not obtain the pH value perhaps due to emergent situation at delivery at that institute. In the revised manuscript, the following comment was added; As the data regarding the umbilical artery pH in 44 cases were not obtained, we used the data from the remaining 222 cases.

We wanted to unify the subjects as typical as possible. This is a reason why chronic abruption was excluded.
4) I have concern regarding the external validity (generalizability) of the study. Given the inclusion criteria, the study is based only on cases where a diagnosis of abruption is confirmed according to placental appearance just after delivery (all ‘healthy’ placentas excluded), and has excluded all cases where the fetus is dead at presentation. The latter is understandable given some of the parameters being studied. However, the retrospective diagnosis of abruption means that this tool cannot be used before delivery. If the tool is designed to be used immediately after delivery, then this should be stated early in the manuscript, as it has important implications for future prospective validation of the tool. The purpose of the tool should be made clearer. There is a danger of the findings being misconstrued unless great care is taken to present the findings in such a way that the narrow remit of the study is very clear, ie, the tool is not intended to be used in cases of suspected abruption, but instead once diagnosis is certain after diagnosis.

Answer: Thank you for your kind advice. According to your suggestion, we have stated that ‘severe abruption score’ is derived from the retrospective diagnosis of abruption and cannot be used before delivery’ in the early part in the Discussion section.

The purpose of the tool was stated in the Discussion section as follows; this score for confirmed cases might be useful for predicting the need for neonatal intensive therapy soon after delivery.

Minor essential revisions

5) It is not clear exactly how data were obtained from case records and by whom, so accuracy of data is not known.
Answer: The detailed information has been exchanged between one of the authors (YM) and doctor in each hospital again and again.

6) The table headings ‘confounding factor’ (table 2 and 3) appear to be inaccurate, as they refer to the variables as potential predictors, not confounders.

Answer: Thank you for your advice. We have changed ‘confounders’ to ‘potential predictors’.

7) Apgar score is not a risk factor for fetal acidaemia.

Answer: Following your suggestion, we have decided to delete the sentence ‘In addition, the Apgar score at 1 and 5 min were significantly lower in cases’ from the revised manuscript.

8) There appears to be some contradiction regarding how the diagnosis of abruption was made, as in the methods section it is stated that the suspected clinical diagnosis was ‘confirmed’ based on placental appearance, while in the discussion section, it is stated that diagnosis was based on ‘classic symptoms and signs’

Answer: We have unified the following sentence as follows; the diagnosis of placental abruption in this study was based on the clinical manifestations, and the placental detachment was confirmed after delivery.

9) I am not sure that it is appropriate to say that the tool created as a result of this study can be used to aid diagnosis of abruption when considering the exclusion criteria ie, the low generalizability.

10) Some of the limitations are clearly stated, but generalizability should be elaborated od (see above)

Answer: As one of the limitations in the present study, the following comment was added;
As a severe abruption score is based only on cases where a diagnosis of abruption was confirmed according to placental appearance just after delivery and is designed to be used immediately after delivery, this score should be used with caution.

11) There are a few minor issues with the use of the English language. Specifically, there is one sentence in the introduction which may prove difficult to understand; ‘It has been reported that placental abruption is as reliable a predictive factors for fetal acidemia as FHR abnormality in both preterm and term infants’, although it appears simply to be due to inappropriate use of the plural ‘factors’. I believe the term ‘mulivariable’ should be used rather than ‘multivariate’.

Answer: Thank you for your advice. We have changed the plural ‘factors’ to the singular ‘factor’. In addition, following the advice of another reviewer, we have changed the following sentence as follows;  It has been reported that placental abruption is a reliable factor for fetal acidemia as well as FHR abnormality in both preterm and term infants. Statistically, the term ‘mulivariable’ is usually used to the term ‘univariate’ comparatively, therefore, we want to use this term.

Discretionary revisions

12) The authors may wish to clarify that the same blood-gas analyzer was used in all 94 institutes.

Answer: We have deleted the words, ‘with a Radiometer ABL-2 blood gas analyzer (Radiometer Co., Copenhagen, Denmark)’

13) The authors have not stated that this is a case-control study (subjects categorized according to outcome data)
Answer: We have changed the sentence in the Methods section, as follows; The approval of the institutional review board (Tokyo Women’s Medical University) was obtained before the start of this retrospective, case-control study.

Reviewer’s report: Kirsty Dundas

1. A very important omission is that there is no comment at any point of contractions.
   
   Rapid frequent contractions often with no resting tone are classically associated with abruption – there can often be seen on a CTG and palpated by midwives/obstetrician – survey this might have been worth looking at.

Answer: Thank you for your advice. We have added the following sentence in the ‘Result’ section. **Although eighty three cases were not recorded mainly due to the emergency nature of the situation without CTG recordings, rapid frequent contractions with no resting tone were observed in 72 out of the remaining 183 cases.**

Introduction:

2-1. para 1 fetal/neonatal is correct MER

2-2. p2 pathological is correct English(CE) MER

Answer: Thank you for your advice. We have corrected them as suggested.

2-3 p2 s2 does not make sense as predictive factors of placental abruption are being investigated – needs explained MCR

Answer: Thank you for your advice. We have changed the following sentence as follows; **It has been reported that placental abruption is a reliable factor for fetal acidemia as well as FHR abnormality in both preterm and term infants.**

2. Methods
3-1. It is not clear exactly where the babies were born e.g. was this all units in Japan or one area? You must state the overall number of deliveries reviewed and thus stated the abrupt rate MCR

Answer: Thank you for your advice. We have changed as follows; The medical records of mothers and neonates in the 94 institutes where these infants were born

And, we have added the overall number of deliveries reviewed and thus stated the abrupt rate as follows; The overall number of deliveries in 94 institutes was 54,628 and the rate of placental abruption was 0.65%.

3-2. p3 – how was placental abruption confirmed after delivery? E.g. was it presence of placental abruption – needs stated for both CS and vaginal delivery MCR

Answer: We have added the following sentence; The presence of hematoma during a cesarean section or coagulation/massive genital bleeding during vaginal delivery was considered to indicate placental detachment.

3-3. p3 there is no information about the mode of delivery of the women at this point MER

Answer: We have added the following sentence; The live fetuses were delivered by cesarean section because of abnormal FHR patterns or maternal indications, such as massive genital bleeding.

3-4. p3 chronic abruption needs defined MCR

Answer: We have added the following sentence; Chronic abruption-oligohydramnios sequence (CAOS) was defined by the following criteria: (1) clinically significant vaginal bleeding in the absence of placenta previa or other identifiable source of bleeding, (2) amniotic fluid volume initially documented as normal and (3) oligohydramnios (amniotic
fluid index $< \text{or} \leq 5$) eventually developing without concurrent evidence of ruptured membranes.

3-5. p3 final sentence – this does not make sense as you cannot ‘confirm’ the diagnosis until after delivery you would not consider giving a tocolytic as this point as this does not need stated MCR

Answer: Thank you for your advice. We have deleted this sentence from the revised manuscript.

3-6. p4 the fetal monitoring definitions are flawed throughout the article and need revised made more accurate. persistent late decelerations are abnormal (not non-reassuring); severe variable decelerations is not a recognized definition – typical or atypical would be more appropriate and again if persistent atypical are abnormal (not non-reassuring); prolonged decelerations needs further refined - $<3 \text{ mins it is non-reassuring but } >3 \text{ mins is abnormal and a bradycardia. Bradycardia is definitely abnormal (not non-reassuring)}$

MCR

Answer: According to your advice, we have reconfirmed the definition. In summary, we have changed the term ‘non-reassuring’ to the term ‘abnormal’. We have defined persistent late decelerations (not deceleration), persistent atypical decelerations, prolonged deceleration ($>3 \text{ mins}$), and bradycardia as ‘abnormal’.

3-7. p6 the terminology of poor (cases) and good (controls) is not clear babies can have ph$<7$ and be clinically well - reword MER

Answer: We have exchanged the order of the sentences as follows; An adverse outcome of the neonate was defined as the occurrence of death before hospital discharge or a diagnosis of cerebral palsy. Then, the outcome of pregnancy was classified as poor (cases) and good
(controls) with a poor outcome defined as a fetal arterial cord blood pH of less than 7.0, irrespective of neonatal outcome.

Results

4-8. p1 of 266 fetuses alive on admission it seems likely that some were delivered dead/born in such poor condition that they could not be resuscitated – this requires comment either way. MER

Answer: We have added the following sentence. In spite of resuscitation, an Apgar score of 0 at five minutes was seen in 7 cases, which resulted in adverse outcome.

4-9. p3 again fetal monitoring definitions, single late decelerations do not occur and if you mean plural then you must say decelerations.

Answer: Thank you for your advice. We have changed singular ‘deceleration’ to plural ‘decelerations’.

4-10. p3 – mode of delivery for all required and outcome of delivery mode sub analyses

Answer: We have changed the following sentences; Cesarean section was performed in 256 patients (96.2%). Of these patients, a neonatal adverse outcome was seen in 18 cases. On the other hand, in the remaining 10 patients who delivered vaginally, a neonatal adverse outcome was not observed.

4-11. p4 unclear are the 43 acidemia patients the poor outcome group – I think the terminology and the English usage makes this a bit difficult to understand MCR

Answer: We think these sentences are understandable without any changes.

These patients were divided into two groups: poor outcome group (case, n=43), and good outcome group (control, n=179). Neonatal adverse outcome cases included 22 patients and
there was a significant difference between cases and controls in the occurrence of neonatal adverse outcome (14/43, 32.6% vs. 8/179, 4.5%, p<0.001).

4-12. p6 fetal monitoring definitions MER

Comment

4-13. p4 FM definitions again MER

Answer: We have replied shown as above.