Author’s response to reviews

Title: High risk pregnancy associated perinatal morbidity and mortality: A second birth population-based survey in Huai’an in 2015

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Author’s response to reviews:

Cover letter-20181228
Re.: PRCH-D-18-01086, High risk pregnancy associated perinatal morbidity and mortality: A second birth population-based survey in Huai’an in 2015

Xiaoqing Zhu, MD; Huiyuan Niu, MD; Hui Wang, MD; Xiaqiong Li, MD; Tingting Qi, MD; Weijie Ding, MD; Liangrong Han, MD; Muling Zhang, MD; Honghua Guan, MD; Shouzhong Li, MD; Chunhong Tang, MD; Yaodong Yin, MD; Xihui Cao, MD; Hong Liu, MD; Cui Gao, MD; Hongni Yue, MD and Bo Sun, MD, PhD

Dear Prof. K Wallace,

Thank you very much for giving us an opportunity to revise our manuscript "High risk pregnancy associated perinatal morbidity and mortality: A second birth population-based survey in Huai’an in 2015" (PRCH-D-18-01086). We have taken all the referees’ comments into consideration in the revision and our revised manuscript (R1) is submitted in both marked and clean versions. All the co-authors have approved the final version.

I hope our reply and revision may satisfy the requirement by both referees and editors. I am looking forward to your decision and any further queries.

With kind regards.

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Authors reply to each query (Q) and additional changes.

To editor’s comments:

Please address the comments made by the reviewers. In addition please ensure that the proper controls were used for the study and are clearly outlined in the methods section.

Response: We interpreted the “proper control” as two aspects. One refers to the whole survey results, and the other to certain part of the sub-population as raised in the last question by Referee 1 (Q7). In general, the survey targeted a sample from the whole birth population in 2015, and all the results were listed in the tables by stratified hospital levels, pregnancy complications, birth weight and gestational age of the total births, delivery modes, maternal age and education years, respectively. Thus variable categories may serve as the corresponding reference to each other. There are also comparisons with data from 2010. We have endeavored to ensure the accuracy of data presentation in the investigation. First, based on the experience of 2010 survey, we included newborns with Apgar score >1 as live births regardless of resuscitation at delivery. Among them, infants who deceased afterwards within 7 days of postnatal life were included as early neonatal death. Second, we defined the numerator of perinatal mortality as the collection of fetal deaths/stillbirths (from 24 weeks of GA in our study), death at delivery, and early neonatal death. Third, we further verified all fetal deaths and stillbirths in all local hospital clinical case records, and modified Tables 2-7 in R1. Corresponding changes are noted in our reply to reviewers’ comments below (Q13-Q15). For the query raised by referee 1, please see our response in Q7 below.

Reviewer reports:

Jonggyu Baek, PhD (Reviewer 1):

This is a well-written manuscript and I agree that this study would provide valuable information for cross-sectional changes and improvement in maternal-fetal and neonatal care in China since 2010. Although I would be more interested in a longitudinal analysis since 2010, I don't have any major comments in the current manuscript. Just a few minor comments are

Q1. A typo %0 should be corrected through the manuscript.

Response: We thank the reviewer for the comments. We have checked the context carefully and any typing errors in the text and tables are corrected with yellow highlight background in the marked version of the revision (R1-marked).
Q2. Sex may be a better term than gender in the current manuscript.
Response: This term has been corrected in the tables and body text in R1.

Q3. On page 7, "Similarly, the rate of fetal death/stillbirth demonstrated a nearly 30% decline in 2015 (2.8% vs. 3.9%)". It is 1% decline of fetal death/stillbirth since comparisons are made over time. Otherwise, the interpretation should be changed in terms of "relative" rate.
Response: this sentence is modified as “…1.1‰ (2.8 vs. 3.9‰), or a nearly 30% relative decline as compared to 2015”, in R1-marked on page 8.

Q4. In Tables, it is not clear how low birth weight is defined. Throughout tables, the cut-off for low birth weight should be clarified.
Response: In the Methods of R1, we have added these definitions on page 6, in Method/Definitions of vital statistics and perinatal morbidities, and in Table 1-8 contents and/or legends for the low birth weight. A new reference (Ref. 19 in R1) is added for the definition of gestational weeks.

Q5. On page 8, "It is obvious that young mother with age <20 years were more likely than older mothers to have preterm and very low birth weight infants". It seems not obvious to me. Table 6 shows that mothers with age > 35 are more likely to have preterm compared to those with age <20.
Response: We thank the reviewer for pointing out this error. Modification has been made accordingly as “mothers with delayed child bearing (i.e. age ≥35 years) were more likely than younger (<20 years) mothers to have preterm and low birth weight infants”, on page 10 in R1-marked.

Q6. The term for multivariate should be changed to multivariable. Multivariate model often indicates when there is more than one outcome variable (e.g., longitudinal outcomes).
Response: The “multivariate” is changed to “multivariable” throughout in the context and tables in R1.
Q7. In the discussion on page 10, "However, in the former group, the absolute number of …., regular and high-quality prenatal visits during pregnancy." Comparison with the absolute number of infants with adverse perinatal-neonatal outcome is meaningless and depends totally on the size of the study population. If the authors try to emphasize that the outcome without pregnancy complications should not be underestimated, then the different control group (or comparison group) should be mentioned.

Response: The proposed “control group” should be used when specific perinatal morbidity or disease is targeted. The current survey mainly focused on the whole birth population, and variables in Table 1-7 were categorized according to hospital levels for delivery, presence of pregnancy complications, birthweight and gestational age strata at birth, delivery modes, maternal age and educational years for comparison. Additional analyses are underway to address sub-populations or patient groups to evaluate the effect of antenatal and intrapartum factors with perinatal and neonatal outcome. Accordingly, the first half of the third paragraph of Discussion, on page 12-13 in R1-marked, is re-arranged and re-phrased, also see Q10 response.

Kishwar Azad (Reviewer 2):

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Q8. Under Vital Statistics of Results. It is not clear what umbilical cord and placenta mean in the context of causes of perinatal mortality.

Response: In R1-marked, on page 9, Results, some of the typical pathological features of umbilical cord and placenta are listed.

Xiangpeng Liao (Reviewer 3):

The authors have conducted a comprehensive regional data analysis of perinatal healthcare system, both for comparing the differences of main results of perinatal healthcare quality between 2010 and 2015, and exploring the relationship between high risk pregnancy and perinatal morbidity and mortality. These data should be important and useful both for quality
improvement and vital statistic. And the data do suggest a significant improvement in perinatal outcome within a typical region, which may partly reflect the situation of China.

Q9. However, there are some key limits to the data quality. As known from the tables, some data, such as fetal deaths/stillbirths, neonatal mortality, congenital anomalies, are highly not in line with the reports of regional, national and international literature. This may due to the fact that the data are mainly based on the routine report of maternal and child healthcare system, other than site investigation.

Response: We agree that our report of perinatal and neonatal death may differ from the domestic reports in that our study design took all those births under 28 weeks of GA, and that all the data were collected from regional perinatal information system, i.e., a study protocol-based complete birth data registry per se, instead of on-site investigational design targeting a specified population from clinical perspectives. We did adopt internationally accepted definitions for fetal death, stillbirth, death at delivery as well as perinatal and neonatal mortality for vital statistics. Many domestic reports on vital statistics were focused on infants with a GA > (or >) 28 weeks of GA (Chinese official domestic definition for birth data reporting), and de facto there were no well-accepted definitions on fetal death, stillbirth, death at delivery, or perinatal death and mortality. This study design was focused on these issues, which may ensure the quality and reliability of the data for reporting. This point is, addressed in the Introduction on page 4, Methods on page 7, and in Discussion on page 11 and 14, by citing reference 14 and an editorial comment (by one of us) on a nationwide stillbirth survey (reference 25), in R1-marked.

Q10. Shortage of full registration of artificial labor to end pregnancy and withdrawal of newborns in early life, is one of main reasons for the data accuracy in China. However, the authors did not explain them. Standard operating procedure and data quality control are also needed.

Response: We agree that it is a domestic problem in reporting fetal death and stillbirth from abortion due to termination of pregnancy due to assisted fertilization during the first and second trimester, and before 28 complete week of gestation. This should be dealt with for understanding the limitation of viability for extremely preterm births. This point is addressed by a sentence added at last para on page 5, of Methods/Study design and protocol, as “Non-medically indicated termination of pregnancy was not included” and as the last sentence of second para of Results/Vital statistics, on page 9, of R1-marked. As indicated in Q9, and on page of 7 in Methods, the quality control for data access procedure was carried out and even at this stage with manuscript revision, we have checked most of the key data regarding fetal deaths, still births and early neonatal deaths including deaths at delivery. We agree that a more on-site SOP for data
access may achieve higher quality. As the current survey comprised >100 sites for deliveries all the year round, our protocol may provide a practical alternative.

Q11. It is suggested that the vital statistics system be discussed in the context, and currently the document cannot support the conclusion: "providing further evidence for the validity and applicability of the study concept and protocol for vital statistics".

Response: In the Background/Introduction, on page 4, first para, we provided the rationale for conducting this survey to further test the concept and methodology by analyzing the regionally complete birth data abased on preliminary vital statistics. In the Discussion, we have rearranged and rephrased the major findings from this survey on vital statistics issue. Following the first sentence in conclusion of Abstract, this speculative statement has been altered as “which should enable more studies using the similar concept and protocol for vital statistics to verify the validity and feasibility”.

Q12. It may be more realistic that using some reasonable data for analysis of individual topic, other than a comprehensive description.

Response: In Discussion, On page 13, first papa, a sentence is added to state that more specific clinical problem-oriented studies should be conducted following this report, which shall include in-utero transport, antenatal corticosteroid use in preterm births, premature rupture of membrane, infection and chorioamnionitis, risks of delivery mode with or without medical indications, etc. as perinatal exposure and outcome measurement for the regional perinatal-neonatal care quality assessment.

Other changes in R1 not related to reviewers’ comments:

Q13. Running head is changed to: Birth population-based perinatal risks and outcome

Q14. On page 9 of R1-marked, para 1 in Results/Vital Statistics, figures of preterm deliveries in level III hospitals are rearranged and rephrased to emphasize more preterm infants were born in level III hospitals in 2015 compared to 2010, reflecting the centralized arrangement of high risk pregnancies.

Q15. Table contents
Table 2, title is modified; definition for low birth weight (LBW) is added in the legends, and data for very LBW and extremely LBW are added.

Table 3-7, title and legends are modified. Variables and values for live births, fetal deaths/stillbirths, LBW are added.

Table 8, title and legends are modified. Categorical variables are modified for clarity.

Q16. Reference 19 and 25 are added in R1 as explained in above response to Q4 and Q9.

All the changes in R1 are marked yellow in word background as added or changed, and red in font as deleted or removed.

Q1-Q12, inserted in body text, denotes the place where corresponding changes to the reply to reviewers’ comments in this cover letter.

For declarations, we have followed the instructions for authors and edited these items as required at the end of body text before the list of references.