Author’s response to reviews

Title: An Adjustable Fetal Weight Standard for Twins: a statistical modeling study

Authors:

Jun Zhang (junjimzhang@gmail.com)
Rafael Mikolajczyk (Rafael.Mikolajczyk@helmholtz-hzi.de)
Xiaoping Lei (leixiaopingde@126.com)
Luming Sun (lumings@gmail.com)
Hongping Yu (yhp268@163.com)
Weiwei Cheng (wwcheng29@163.com)

Version: 3 Date: 17 May 2015

Author’s response to reviews:

Dear Editor:

Thank you very much for your and reviewers’ comments. They helped us to improve the manuscript substantially. The following are our point-by-point responses to these comments.

Editor’s comments

As you can see, Reviewer 1 has concerns about the clinical impact of this work. We did seek external advice from one of our Editorial Board Members, who said that the clinical impact of the work is sufficient to warrant further consideration in BMC Medicine. However, I would please request that you comment on these concerns in your revised manuscript, and make very clear the importance of your work.

Response: Thank you for giving us another opportunity to address the issue of clinical importance. We have added relevant information in the Discussion as follows:

Finally, a recent fetal growth study collected data in healthy, well-nourished women living in environments with minimal constraints on fetal growth, across eight geographically diverse urban areas worldwide.24 The results showed substantial variations in fetal size at birth among races/countries. For example, the singleton mean birthweight at term in India was 2.9 kg while the corresponding birthweight in U.K. was 3.5 kg,24 suggesting that there are substantial differences in fetal growth potential among races that cannot be explained by environment.

Conclusion

It is a common practice to use a singleton fetal growth standard to assess twin growth, which could substantially misclassify a high proportion of twins as growth restricted. Furthermore, there are differences in twin fetal size among races and
populations. The adjustable fetal growth standard for twins is a flexible tool and can be used in different populations as a standard or population reference. It can reduce the misclassification of abnormal fetal growth and provide more accurate fetal assessment.

In addition, please also add more detail to your methods. You have stated that 'Detailed description of the methodology has been provided elsewhere' citing your previous work in the Lancet. However, this detail must also be present in the current manuscript.

Response: Yes, we have added detailed description of the study methodology in the Methods section (Page 5 – 6).

Reviewer 1’s report

This is an interesting study, very similar to the one previously published by the same group aiming singleton pregnancies (1). Authors must discuss about other perspective to the same problem. Is a reference curve for twins or adjusted by ethnicity really necessary/useful? Cohorts of healthy, well nourished, pregnant women from eight geographically diverse populations who were at low risk of adverse maternal and perinatal outcomes shows similar fetal growth pattern and no need for locally adjusted charts (2).

Response: The Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project (Lancet 2014;384:869-79) did not present fetal growth patterns separated by different countries. It was another paper published by the same study group (Lancet Diabetes Endocrinol 2014(10):781-92) that separated the data according to geographic locations. It showed that the singleton mean birthweight at term in India was 2.9 kg while the corresponding birthweight in U.K. was 3.5 kg, suggesting that there are substantial differences in fetal growth potential among races. However, the authors used crown-rump length and head circumference as indicators to claim that there was no significant difference in fetal growth among countries. Such a conclusion was criticized by other investigators with more convincing evidence and arguments (Lancet Diabetes Endocrinol 2014(10):773-4). In the authors’ reply, they acknowledged that “We did not state that there are no differences in fetal growth across our eight free-living study populations because differences were obvious and inevitable.” (Lancet Diabetes Endocrinol 2014(10):774-5).

Additionally, the use of several charts may be a source of error and confusion: the same woman might be classified as having intrauterine growth restriction or a normal gestation depending on the chosen chart; such choice is an arbitrary decision made by the professional performing the ultrasound scan, which might be particularly difficult for pregnant women (or even fetuses) with mixed ethnicity. Moreover, much of the difference in the reference charts among countries and even between twins and singletons might be related to different proportion of diseases and nourishing conditions.

Response: We respectfully disagree with this comment. The “one-size-fit-all”
approach, though simple, may result in substantial misclassification of abnormal fetal growth in certain population. For example, most ultrasound-based fetal growth standards were created in developed countries based on Caucasian population. When such a standard is applied to an Asian population, say to India with a mean birthweight of 2.9 kg, a large proportion of the fetuses are classified as growth restriction. The adjustable growth standard overcomes this shortcoming.

References

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician

Reviewer 2’s report

Abstract

Results section: the following text “The discrepancy was probably due to errors in gestational age in these studies.” is not properly a result of the study, it is more suitable in the “discussion” section.

Response: We have deleted this sentence.

Methods

Several studies have described that growth pattern is similar between singleton and twin pregnancies up to the end of the second trimester. However fetal growth seems to decelerate afterwards. Is it valid to apply the proportionality principle on a formula which is based on ultrasound derived singleton pregnancies? Hadlock’s formula describes growth pattern in singleton pregnancies and does not take into consideration the deceleration that occurs in twin pregnancies in the third trimester.

Response: This is a very good point. We have added a paragraph in the Discussion to address this question:

“Studies have shown that singleton and twin growth patterns diverge in late pregnancy.2-4 Why then did the adjustable twin standard that is derived from the singleton growth equation match the observed data seamlessly? One explanation is that twins may have a consistently slower growth velocity than
singleton. At early gestation when fetuses are small, two curves are very close. As the fetuses become larger and larger, the difference in fetal size emerges and becomes bigger with gestation.”

Results

Figure 1 compares observed and adjusted fetal weight standards for the US Database. Why did the authors not present and compare the upper (90th centile) and lower (10th centile) limits observed and adjusted curves in this figure?

Response: We have added the 10th and 90th percentile curves as suggested (Figure 3).

Discussion

Can the authors hypothesize the reason why the 90th centile observed in the Brazilian longitudinal data was greater than what was predicted in the model? I believe one would expect the standard deviation to be narrower in longitudinally derived data.

Response: It is a good observation. We cannot come up with a satisfactory answer. Our method has a fixed standard deviation, i.e., the distances between 10th and 50th percentiles and between 50th and 90th percentiles at a given gestational week are exactly the same, i.e., a true normal distribution (Figure 5). In the Brazilian longitudinal study, the distance between 10th and 50th percentiles is the same as ours but the 90th percentile curve is higher than ours, suggesting that the distribution of their data may not be totally symmetric. Nonetheless, the difference was small.

Minor Essential Revisions

The text should be reviewed for several typo mistakes. Essentially the are spaces missing between words. Examples in page 5: “twin births at term” “Hadlock's curve” “percentiles can be calculated A complete fetal weight standard”.

Response: This may be due to an incompatible version of the software. We have corrected these typos.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests

We hope that our revision has thoroughly addressed the reviewers’ comments. Should further changes be deemed necessary, please do not hesitate to let me know.
Sincerely,
Jun Zhang