Author's response to reviews

Title: Adverse maternal outcomes associated with fetal macrosomia. What are the risk factors beyond birthweight?

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Author's response to reviews: see over
Dear Editor,

Thank you for the initial examination of our manuscript. We have prepared a revised version addressing all the specific issues raised by the reviewers and yourself. You will at the end of this letter a response to the referees describing our responses point by point. We have also carefully gone through the manuscript to make the appropriate substantive changes, which are underlined and in bold. We have reviewed the Journal’s current author’s guidelines. All the authors have read and approved the revised version of the paper.

We would like to thank the reviewers for their pertinent comments. We have considered their suggestions and we think that the changes they requested have enabled us to improve the manuscript.

We do hope that our paper now meets the standards of publication of BMC Pregnancy and Childbirth and we are looking forward to your decision.

Sincerely yours

Florent FUCHS, MD
Point-by-point reply page

Below are listed every comment and changes made in the text:

Editor's comments:
The objectives of this study are clearly stated and the conclusions are supported by results. The main strength of this study is the large sample size. The reviewers need to resubmit their paper after answering the queries of the reviewers and including other confounding variables in their multivariate analysis. The paper should be edited by a native English speaker. According to your wishes, we have including other confounding variables in the multivariate model. The paper has also been edited by a native English speaker.

Reviewer: 1
The objectives of the study are clearly defined. The methods are appropriate and well described. The results reached are consistent with other studies in the literature. Data is appropriately collected and reported. The conclusions are well balanced and adequately supported by the data. Limitations of the study are not adequately addressed. The literature review is appropriate. The title is better changed to "What are the risk factors beyond birthweight?"
As suggested by the reviewer, the title has been changed

Although the approach of this study is new, however, the risk factors identified were commonly reported in the literature and the risk factors could stand out on their own when multivariate analysis was utilized including birthweight. What is important in this study is the big number of macrosomic infants included.

I have the following comments that require discretionary revisions:
-Prolonged labor was defined as >10 hours, is there a reference to support this definition? No. Duration of labor was a continuous variable that was then summarize into three categories (<5 hours, 5-9 hours, and >10 hours). As odds ratio for the prediction of MC were similar for the two first categories, we made the variable dichotomous. For easy spelling, we called duration of labor >10 hours: “prolonged labor”.

-Factors that affect the incidence of lacerations or bleeding like parity, episiotomy, fetal position, instrumental delivery and the use of epidural were not included in the multivariate analysis
We did not include all these parameters for different reasons: Parity had been included afterwards in the revised version. We had no information about fetal position or epidural. Episiotomy (corresponding to 2nd degree perineal laceration) was not included because 3rd and 4th degree laceration were part of the composite outcome in MC. Instrumental delivery was not included as we included the variable “cesarean during labor” and those two parameters were collinear.
- Since the combined attributable risks constitute around 42% of attributable risk, it is worth commenting that most of the cases of MC are not associated with identifiable risk factors. We agreed with that comment. We have mentioned it in the discussion (last paragraph in the discussion).

- It is mentioned that labor was induced for postdates in 60% and for maternal fetal complications in 30%, were the rest for social indications? No, other indication were premature preterm rupture of membranes (10%).

- The rate of CS in labor is 17% which appears quite low even in non-macrosomic infants. What is the rate of CS in the hospitals included in the study? In those two hospitals during the study period, the global rate of CS (elective+ during labor) was respectively 29.2% and 30.1%. Those percentages are in accordance with the ones observed in tertiary care center in France according to French national perinatal survey[1].

- In table 1, mean and range is mentioned; usually median-range. Variables that have Gaussian distribution are described in mean +/-standard deviation, which is the case for age. We added the range in order to have an idea of it for this particular parameter.

Minor Essential Revisions

Abstract

Background

“To identify risk factors, beyond fetal weight, associated with adverse maternal outcome in delivering infants with a birthweight of 4000g or greater and to quantify their role in maternal complications”. Long sentence, need to split into two statements.

Methods

“All women (n=1564) with … has been included” replace has with have

Results: Need to lump risk factors that increase the risk of maternal complications together (i.e before previous macrosomia)

Conclusions: Can change to: “In women delivering infants with a birthweight of 4000g or greater, some maternal characteristics as well as labor parameters may worsen maternal outcome beyond the influence of increased fetal weight”

Background:

“adverse neonatal outcome including stillbirth, neonatal mortality” add “and” before neonatal mortality

“with and without new born over 4000 g” change to newborns

“to other risk factors than fetal weight” change to risk factors other than fetal weight

“occur in women delivering macrosomic infant” add s to infant

“risks factors of maternal complications” change of to for

“who delivered macrosomic infant” add s to infants

Methods

“A systematic adjustment was made for hospital centre,” Delete,
“In the one hand, they may prevent maternal complications (in particular perineal lacerations), in the other hand” replace in with on –“‘on the one hand” and “on the other hand”
“one with the same composite criteria for MC, the other including elective cesarean delivery for macrosomic suspicion as a supplementary criteria for MC.” Replace one with the first and the other with the second

Table 1. 696 (44,.5), delete .
Gestational diabetes under diet-change to diet-controlled gestational diabetes
3rd or 4th degree perineal tears§; § is not explained
(1564 women with singleton pregnancies who attempted a vaginal birth and delivered infants weighing at least 4000 g, elective cesarean excluded)-no need to include in table
“cesarean during labor and birth weight greater than 4,5 kg” change to grams to be consistent

Discussion
“women with an history” replace an with a
“Over those two steps, complications are dramatically increased. The 4500 g threshold was always present in our study, but to a lesser extend since the sample was limited to newborns heavier than 4000 g.” replace steps with thresholds and extend to extent
“results potentially generalizable” add that are potentially…..
“These singularities in body tissue” replace singularities with particularities
“more prone to returned for a uneventful second delivery.” Unclear, can change to “are more likely to experience an uneventful second delivery”
The whole paragraph starting with maternal diabetes has to be modified.
[30, 31] missing period
Change main “provider” to main “contributor”
Agreement with literature, add the
“the magnitude of the proportion of MC that could be avoid in removing the risk factor” changed avoid to avoided
“for factors that may be removed, but to a lesser extend for unchangeable factors such as ethnic origin.” Replace removed with modified and change extend to extent
“Estimation of attributable risks enabled us to precise that only 10% of MC” change precise to precisely identify
“identical to prolonged labor” change to identical to the contribution of prolonged labor

Conclusion
“Obstetricians should pay attention to these parameters that could led” change to should be aware to these parameters that could lead”

For all these changes, we totally agreed with the reviewer and we made the changes in the text.

Reviewer:2
Major 1. history of macrosomic infant vaginally delivered is confounded with parity. The authors should test this by creating a three level variable for nulliparous, multi - macro and multi+ macro and report their findings.
We totally agreed with that comment and as suggested by the reviewer, we created this variable and added it in multivariable regression model instead of “history of macrosomic infant vaginally delivered” alone.

**Major 2.** Duration of labor and cesarean delivery during labor are potentially confounded and could be substantially colinear. Prolonged labor is a major reason for non-elective cesarean delivery. This should be investigated and reported. Cesarean delivery is a confounding factor for the relationship between duration of labor and MC. To control for confusion we added both parameter in multivariate model. No colinearity was found in the model.

**Minor 1.** How similar are labor induction and gestation as three categories of <37 weeks, 37-41 weeks and >42 weeks?
We could not test these hypotheses as we only had 1 delivery <37 weeks and 4 deliveries >42 weeks.

**Minor 2.** Clarify whether body mass index is a continuous variable or categorical reflecting obesity.
We changed the variable name in multivariate analysis into “obesity (body mass index >30kg/m^2)” in order to make it clearer.

**Minor 3.** Justify that the differences reported for Asian are not merely opportunistic. Is there a reason that Asian would be expected to be different.
As mentioned in the text, perineal tissues of Asian women are frequently flimsy and more prone to tear. We believe that could be one of the explanations.

**Minor 4.** The cutoff for macrosomia has been selected as 4000 g. How would the results have been impacted if >4500 g were chosen to specify macrosomia as other studies have done?
Such an analysis is not possible with our data as we only had 126 patients delivering babies weighing >4500g. Our results would be underpowered.

**Minor 5.** Clarify if episiotomy was part of standard procedures for women in danger of perineal tears. The combined 63% of women with tears is very high and needs explanation.
We agreed with the reviewer about the fact that 63% of patients with 1st or 2nd degree tear is very high. However those results nearly reach the results of other French maternity according to French national perinatal survey[1]. We had no policy of systematic episiotomy; however, it is too frequently performed in France even if it is well known not to reduce the incidence of 3rd or 4th degree perineal tear.

**Minor 6.** How many of the 261 women with postpartum hemorrhage required blood transfusion?
Among the 261 women with PPH, 23 of them (9%) required blood transfusion.
Minor 7 were maternal diabetes and body mass index colinear. Have these effects been tested in models with and without birth weight? They could be more useful predictors of maternal complications than birth weight.

Those two parameters have been tested and we did not find any colinearity in our sample. However the proportion of maternal diabetes and obese patients remained even though relatively low in our sample (respectively 7.3% and 11.5%) and that is probably why they did not reach significance.

Minor 8. how can attributable risk be used in prevention when applied to high birth weight, prolonged labor or cesarean section

Attributable risks are here to quantify the magnitude of the proportion of MC that could be avoided by removing the risk factor. These results may change the individual practice of one’s obstetrician when taking care of a patient with a macrosomic infant. Elective cesarean section; reduced duration of labor before performing CS; looking at women’s ethnicity… could be one of the different evolution.

Minor 9 why is there no mention of neonatal morbidity in the text?

We apologize for that point and added information about neonatal morbidity in the results part.