Title: What is the impact of interventions that prevent fetal mortality on the increase of preterm live births in the State of Sao Paulo, Brazil?

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Author's response to reviews: see over
Dear Editor

Prof L. Lewis Wall and Mr Ian Dominique Trinidad,

Thank you for your letter of 11th of November, which we attach. As suggested, we edited and reformulated the manuscript submitted earlier (1083842410122116) We included recommendations of the reviewers, and changed the manuscript title (What is the impact of interventions that prevent fetal mortality on the increase of preterm live births in State of Sao Paulo, Brazil?) in order to clarify the main objective of the study which was analyzing time trends in fetal and preterm births in Sao Paulo State. We think that the new manuscript makes a fundamental contribution to the understanding of the increased frequency in preterm births in middle income countries.

As suggested by one of the referees we also included data on cesarean section deliveries by gestational age groups. We agree that this strengthens the case for the hypothesis of the decline of stillbirths as a contributor to the increase of idiopathic preterm births during the period analyzed. We are submitting also the answer for the comments of the reviewers.

We also considered the revision required and some changes to the manuscript related to: line numbering, title page, and the sessions: abstract, competing interests, author’s contribution and acknowledgements.

Best wishes,

Marcia Furquim de Almeida

Corresponding author
Letter received from the Editor

De: "BioMed Central Editorial" <editorial@biomedcentral.com>
Para: "Dr Marcia Almeida" <marfural@usp.br>
Enviadas: Terça-feira, 11 de Novembro de 2014 22:40:44
Assunto: 1083842410122116 - Increase of preterm live birth...

Re: MS: 1083842410122116
Increase of preterm live births and the decline of fetal and neonatal mortality in Sao Paulo state, Brazil
Gizelton P Alencar, Zilda P Silva, Felipe P Nascimento, Patrícia C Santos, Priscila Raspantini, Barbara L Moura, Laura C Rodrigues and Marcia F de Almeida
BMC Pregnancy and Childbirth

Dear Dr Almeida

Thank you for considering BMC Pregnancy and Childbirth for your manuscript above. Peer review of your manuscript is now complete and, in the light of the reports, I am sorry to say that we cannot consider the manuscript for publication and are closing your file. The reviewers' comments are accessible in PDF format via the links at the bottom of this email. Please contact systemsupport@biomedcentral.com if you have any problems opening the files. Please also take note of the editorial comment below.

Editorial Comment:
This topic is potentially interesting. However due to the way in which the authors analyze the data the conclusions cannot be supported. I suggest the authors revise the paper by taking into account all of the recommendations made by reviewers.

Please note that we think it may be possible to revise your manuscript to address these comments but that this would require longer than our standard revision period. However, we are willing to consider your manuscript further once all the concerns have been addressed. Therefore, if you are able to address all of these concerns, please do submit a new manuscript to BMC Pregnancy and Childbirth. If you are able to do this, a full covering letter, explaining the revisions made, should accompany the submission.

Please note that this decision applies across the BMC-series of journals (http://www.biomedcentral.com/info/authors/bmcseries#journallist). Therefore, if you were to submit your revised manuscript to another journal within the BMC-series, your submission should also be accompanied by a full covering letter.

Thank you for your interest in BMC Pregnancy and Childbirth.

Best wishes,

Mr Ian Dominique Trinidad
on behalf of Prof. L. Lewis Wall

e-mail: editorial@biomedcentral.com
Web: http://www.biomedcentral.com/

Referee 1:
http://www.biomedcentral.com/imedia/1798150177148036_comment.pdf
Referee 2:
http://www.biomedcentral.com/imedia/1120071761146679_comment.pdf

Additional material submitted by the reviewers
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Reviewer 1: Marcelo Z Zubaran Goldani

Introduction

1-The author omitted some important references showing that changes in preterm, and perinatal rates is vast and complex phenomena in Brazil involving a number of factors.

Reply: we thank you for the references; we incorporated when relevant in the paper.

2-Preterm or prematurity?

R: Both terms are used in the literature. We choose to use “preterm”. The definition of preterm births is based on the gestational age.

Methods

1-Foetal mortality rate was calculated wrongly: FMR= nº deaths/ total number of gestations.

R: We did not use the foetal mortality rate, we used the foetal mortality ratio to make it comparable to neonatal mortality rate, as both were measured with the same denominators. We made it clearer in the methods section.

2-The rates (fertility and others) and covariates were poorly described;

R: We included the definition of fertility and neonatal morality rates.

3-Fertility rate was misused in this contest considering only # 35 years old. Its well known the intense demographic transition in Brazil considering maternal age. Thus, it’s necessary to analyse the importance of these changes on the outcomes specially related to adolescent mothers.

R: We considered only 35+ year olds because we are interested in fetal mortality. The fetal mortality Ratio (FMRatio) is substantially higher in women in 35+ years old only. It is true the FMRatio is high also in adolescents 10-14 but numbers are very small (16 in 2000 and 6 in 2010, in Sao Paulo state). The FMRatio of 15-19 is very similar to women 20-34 (Table below). So, although we agree the demographic transition is important in Brazil, and fertility rate trend is decreasing in adolescents and increasing in 35+, we do not believe that changes in adolescents births are relevant to understanding the changes over time in fetal mortality.

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>2000</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 14</td>
<td>17,37</td>
<td>6,97</td>
</tr>
<tr>
<td>15 - 19</td>
<td>8,00</td>
<td>4,35</td>
</tr>
<tr>
<td>20 - 24</td>
<td>6,44</td>
<td>3,95</td>
</tr>
<tr>
<td>25 - 29</td>
<td>5,94</td>
<td>3,43</td>
</tr>
<tr>
<td>30 - 34</td>
<td>7,66</td>
<td>3,52</td>
</tr>
<tr>
<td>35 - 39</td>
<td>11,78</td>
<td>5,44</td>
</tr>
<tr>
<td>40 - 44</td>
<td>18,11</td>
<td>7,87</td>
</tr>
<tr>
<td>45 - 49</td>
<td>36,00</td>
<td>9,46</td>
</tr>
<tr>
<td>Total</td>
<td>7,58</td>
<td>4,10</td>
</tr>
</tbody>
</table>

Source: Ministry of Health of Brazil.
4-Why was the impact of type of delivery section on the outcome not included in the analysis? It’s well known the significant impact of Cs on the outcome, especially considering the high rates of CS in Brazil

R: Thank you for the suggestion. We included in the analysis the caesarean section delivery by gestation age for live births for which it is available and had a good quality of information.

5-It’s important to observe the birth weight in the gestational age’s groups and modifications during the time series. What was the lowest birth weight considered in the analysis?

R: The choose to include gestational age rather than birth weight because gestational age is more reliable than birth weight for fetal deaths.

Results.
6-The reduction of FMR presented a peculiar pattern - higher in early gestational ages. The explanation was insufficient and any possible bias or data inconsistencies were not considered in this case.

R: Thank you for your suggestion. We did investigate this further and noticed that the proportion of c-section is increasing faster in young gestational ages (as presented in the new Table 1 in the paper) and included in the discussion the suggestion that the decrease in earlier gestational ages is in part consequence of more frequent appropriate early intervention.

7-The trend of FM mortality was not linear, mainly in > 28 foetus, which has a peculiar trend: very intense the first years and reducing afterwards. The year of 2005 changed the trend in all ages. Why?

R: We used the exponential regression, not a linear regression. We do not have an explanation for the variations in the trend year by year.

8-Table 2 <36?

R: Thanking pointing the typo. We corrected it.

8-The results (table 2) showed a number of possible confusion or interaction effects which were not investigated. It’s possible that maternal education effect on outcome can be mediated by prenatal care, for instance.


9-Conclusion
The results didn’t sustain the conclusions of the study. Prenatal care and changes in reproductive profile per se cannot justify the trends. Thus, the rationale used in the analysis and discussion do not account for the findings. Other studies, cited above, showed a very complex scenario related to demographic and epidemiologic transition in Brazil involving preterm birth and infant mortality, which was not considered properly along the article
R: The study was fully revised and included information on caesarean section deliveries by gestational age. We included in the discussion the demographic transition in Brazil.
Reviewer 2: Jorge Lopez-Camelo

1-The Pearson’s correlation Method to associate two proportions is not appropriate, since does not meet the assumptions of normality and linearity to apply this type of test. I suggest that the authors use Spearman non parametric

R: The correlations presented are between trends (over each year from 2000-2010) in those variables not proportions between the variables. We made this clearer in the text.

2-An example of inconsistency between the relationships of variables is:
2.1 the preterm birth prevalence increase when decrease the frequency of inadequate prenatal care (less than 4 visits according to definition of the authors).
2.2 PTB prevalence increases with multiple pregnancies, but multiple pregnancies decrease with frequency of inadequate prenatal care. How explain this observations?

R: We do not think there is an inconsistency. Both mother with multiple pregnancies are more likely to have preterm deliveries and more adequate prenatal care because of their conditions. We do think that we were not clear enough in the text and we have rewritten this paragraph.

3-In this way I have concern with the method to evaluate secular trend. The determination coefficients (R2) are very high, probably indicating an override of the model. I suggest reviewing residual of the regression.

R: The regression considered each of the measures (fetal mortality ratio, neonatal mortality rate, proportions of preterm births) as the response variable and the years from 2000 to 2010 (year) the explanatory variable. We evaluated the residuals of the three models in terms of a normality test of the residuals (Shapiro-Wilks test) and a residual-versus-fitted plot. The p-value indicates no rejection of the null premise (normality), so the normality was satisfied. We also believe that the residual plot shows no apparent pattern.

4-In material & method, total number of births is not shown.

R: The total number of births was: 667033 (2000) and 603746 (2010). We included the total number of preterm live births and fetal deaths in the Results.

Discussion

5-The authors argue: “The group of characteristics studied showed a strong correlation with each other in the period analyzed, indicating the presence of an association between their behavior throughout time and the increase in preterm births and the decline of fetal deaths”. Is not clear how they arrive at this conclusion. The changes of pregnant profile were not analyzed over time.

R: We did include the analysis over time in the text but not in the figures. We have now included an analysis with the c-section rate by gestational age.

6-The authors argue: “The present study was performed with secondary data files and confounding variables that were not possible to be controlled may be present. Although the data available does not enable the assessment of the etiological complexity of preterm births, the temporal analysis of these data suggests that the growth trend of preterm births is partly due to the increase of medically indicated”. I understand that any confounding was controlled in the analysis of secular trend. On the other hand, it were not evaluated subtypes clinical of
preterm births, therefore, the argument is not supported by the analysis of the results. In this way the authors argue “

*R: We agree that it would be very interesting to analyse the data separately for Preterm resulting from clinical interventions, premature rupture of membrane and spontaneous preterm. However, these data are not available in the routine files. We do believe however that the data available sheds useful light into the questions studied. We have redrafted the discussion and conclusions.

7-The present data suggest that clinically indicated preterm births may be playing a role in the growth of preterm live births, explaining a maximum of 45% of its growth”. How the authors arrive at this conclusion, how was calculated 45% of total secular trends ?. I don’t understand.

*R: We edited the text to make this clearer and now it reads as: During the period studied, there was a reduction of 1,604 fetal deaths, and an increase of 3,548 preterm live births. If all the reduction in fetal deaths were the result of a successful intervention leading to a live preterm birth, this would correspond to an additional 1604 preterm births. This would explain 45.2% of the increase in preterm births over this period. This value represents the maximum contribution of successful interventions to prevent a fetal death on the increase in preterm live births, and it is likely that the contribution is less than this maximum value.

8-Table 1: the reference 1 and 2, doesn’t report in the bottom of table. The fertility rate is expressed in percentage?
*R: We have explained in the text how we fertility rate was expressed and have added to the footnotes of table 1.

9-Table 2: the correlations between variables are extremely high, again I suggest reviewing the statistical analysis.
*R: Table 2 shows the correlation in time trends in the variables, not the variables themselves. We edited the title of the table, the methods and the results to make this clearer.

10-The figure 4 is not clear. Tittle “Distribution of pregnancies according to fetal deaths, preterm LB and at-risk fetuses. State of São Paulo, Brazil. 2000-2010. What means at risk fetuses in the graphic?
*R For the whole paper we changed the term ‘fetus at risk’ to pregnancies/gestations at risk, and explained the concept more clearly in the methods. The text now says: “A proxy for the total number of pregnancies was obtained from the sum of live births and fetal deaths for 2000 to 2010. We treated all the pregnancies as at risk of two outcomes: fetal death and preterm births. This was considered as a gestation cohort, where the denominator was the total number of gestations at each gestational age, according to the definition proposed by Joseph et al [7]. The estimate of survival rate according to gestational age group was calculated and the proportions of preterm fetal deaths and preterm live births pregnancies were obtained.”