Author's response to reviews

Title: Factors associated with tocolytic hospitalizations in Taiwan: evidence from a population-based and longitudinal study from 1997 to 2004

Authors:

Ke-Zong Ma (kezong@kmu.edu.tw)
Edward C Norton (ecnorton@umich.edu)
Eing-Mei Tsai (tsajeing@yahoo.com)
Shoou-Yih D Lee (sylee@email.unc.edu)

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Author's response to reviews: see over
Dear Dr. Norton:

Enclosed please find my revised manuscript, "Factors associated with tocolytic hospitalizations in Taiwan: evidence from a population-based and longitudinal study from 1997 to 2004," which is co-authored with Edward Norton, Eing-Mei Tsai and Shoou-Yih Daniel Lee.

We have added several references as suggested and revised our abstract, introduction, methods, results, and discussion. The National Health Research Institute in Taiwan provided approval for the use of the data in this study. All changes in our manuscript are in red font. Please refer to the next page for our point-by-point responses to the reviewers’ comments.

Please contact me if you have any problems or questions. Thank you for your consideration.

Sincerely,

Ke-Zong Ma
Assistant Professor
Referee 1

Major Compulsory Revisions:

The description of data analysis using the probit model tends towards a reader with statistical knowledge or expertise. While detailed, it is potentially confusing to a reader without such knowledge and may impact on the credibility of the results presented in this paper. I would suggest, recognising the necessity for statistical formulae, to provide a plain language summary of the probit model to further enhance an understanding of this model for potential readers.

Response: Following the reviewer's suggestion, we added a brief description of probit models in the Method section. The relevant text now reads as follows (page 8):

“Because the dependent variable (having a tocolytic hospitalization) was binary, we estimated a probit model for this outcome. The probit model is a popular specification for a binary-response model that emerges from the normal cumulative distribution function (CDF). The probit model on the full sample was to predict the probability of a tocolytic hospitalization. In this model the probability will lie between 0 and 1 and vary nonlinearly with the explanatory variables. These properties are in contrast with the linear probability model where the probability increases linearly with the explanatory variables and may lie outside the 0-1 range.”

In the 'background' section of this manuscript the authors refer to two recent developments in Taiwan that make this study interesting....it is for these reasons that I questions the study's relevance to populations and/or health care systems/providers outside of this country. while interesting, of significance and worthy of future research, the findings of this study are not generalisable to the wider population outside of Taiwan. This is a major limitation to this study that requires recognition.

Response: We agree with the reviewer that this might be a limitation of our study, and we have recognized this limitation in the discussion section (page 11).
Minor essential revisions:
Page four of the manuscript states 'the total fertility rate dropped from 1.760 in 1996 to 1.180 in 2004'. What do these figures allude to? e.g. 1.760 per x amount of the population etc. This needs to be made clear to the reader.

Response: That’s a good suggestion. We used the number of births instead of the total fertility rate so this sentence will be clearer to the readers (see page 4).

“The number of live births in Taiwan was 325,545 in 1996, and it decreased to 204,414 in 2007 [22], giving Taiwan one of the lowest fertility rates among developed countries [23].”

Table 1 requires further clarification as to the figures provided, e.g. the figures provided for Age and Wage - clarify if these relate to the mean in the table, Having a major disease card - e.g. does the figure provided indicate N of the total population who gave birth, etc.

Response: We rewrote the second paragraph of the results section (page 9), which provided a description of patient characteristics such as wage, age, and having a major disease card.

“The descriptive statistics in Table 2 indicate that women experiencing tocolytic hospitalizations were generally older (29.1 vs. 28.2 years old), had poorer health status in terms of having a major disease card (2.1% vs. 1.3%), had prior pregnancy-associated hospitalizations (38.2% vs. 3.6%), and had higher inpatient expenses in the previous year (NT$3968.9 vs. NT$3637.2), compared to all women who gave birth. Women experiencing tocolytic hospitalizations also had higher wages (NT$18393.5 vs. NT$17202.9). The last column of Table 2 showed the descriptive statistics about the excluded population, and they were also older and unhealthier compared to the general population.”

Referee 2
Major Compulsory Revisions
Abstract
1) The use of tocolytic hospitalization in antenatal care is certainly controversial but I do not think one could say that it was “understudied”, so this would need to be changed in the abstract.
Response: We have replaced “understudied” with “worthy of more research” (see abstract).

2) “The decline in fertility significantly increased the probability of tocolytic hospitalizations” is too strong a statement, based on the data. Including the decline in fertility in with the other factors that are listed as “associated with” hospitalization would be better.

Response: We revised this sentence as the reviewer suggested (see abstract).

Background and discussion
3) There is a wealth of literature on this topic, but much of it has been omitted from the paper. In general, the references quoted appear to be rather dated. For example, seven of the ten refs in the initial review (2-11) are from 1992-1999. Other, more modern refs would also be appropriate here e.g. Parry et al 2006, Fox et al 2007, Gilbert 2008, Parant et al 2008. (If the authors wish to indicate the state of research prior to the conduct of the study, i.e. 2004, then it may be acceptable just to include more up-to-date work up to 2004, but the other studies should then be included in the discussion).

Response: We have added references suggested by the reviewer.

4) The references to support the statement “antenatal hospitalizations with a pregnancy-related diagnosis impose significant health, economic, and psychosocial burdens on pregnant women” are from 1996 and 1987! These are too old, especially given that the authors are writing about economic and psychosocial costs that will have changed over the 1-2 decades since the papers referred to were published. The Cochrane review by Sosa et al 2004 might be a suitable replacement.

Response: We have dropped the 1987 citation and replaced it with more recent references in the introduction, including the Cochrane review by Sosa et al 2004.

5) “Tocolytic treatment, which uses pharmacologic agents to inhibit uterine contractions and to prevent delivery before the completion of 37 weeks of gestation, is touted to reduce perinatal morbidity and mortality associated with
threatened preterm labor” – needs a reference to one, or more, of the many Cochrane reviews on this topic.

Response: We cite two references by Maloni et al. in 2001 and 2002 for the definition of tocolytic hospitalization in our study.

6) The reference quoted for the decline in fertility rate is a secondary one, and is also out of date, based on a fertility rate in 2004. The fertility rate in Taiwan was 1.1 in 2007 (statistics obtained from the governmental website http://eng.stat.gov.tw/public/Data/87311841271.pdf). (I appreciate that the data were collected up to 2004, so perhaps a fertility rate of 2004 is appropriate to quote, but it should come from the government statistics and be followed by a reference to the latest (2007) rate, to indicate that this is still a factor of interest.)

Response: We now use the number of births from 1996 to 2007 instead of the total fertility rate from 1996 to 2004 in the introduction (page 4). The direct source of the statistics, a government website, is cited.

7) Re “evidence that for women with preterm labor, tocolysis is frequently unnecessary, often ineffective, and occasionally harmful” - one reference quoted is from 1973, and all three are single studies or opinion pieces. That is not really convincing evidence. There are a number of Cochrane reviews on this topic and they need to be read in detail and used throughout this paper as they contain the best evidence available at present.

Response: We have replaced the old referenced with the recent Cochrane reviews.

8) “Other options to constrain overutilization include the application of technology (e.g., the use of testing such as fetal fibronectin)” - the authors would need to refer to recent reviews on this topic such as that by Smith et al (2007).

Response: We have cited Smith et al.’s paper as suggested (page 14). Other recent reviews are also referenced when appropriate.

9) One major limitation of the work that needs to be clearly stated is that these data stem from 2004, five years ago, and much may have changed since then.

Response: We recognized this limitation in our discussion (page 11).
Discretionary Revisions
Following a thorough perusal of the Cochrane reviews, the authors may wish to change, re-word or adapt their conclusions.

Response: The Cochrane reviews provided more recent evidence on the effectiveness of tocolysis. They are referred to in the revision.

Minor Essential Revisions
Second line of results “tcolytic” needs an “o”

Response: We have corrected this typo.

Referee 3:
1. The authors have excluded many of the conditions that are associated with high-risk deliveries, including multiple births. While I can understand why they did this, it also makes it hard to put many of the findings that they report in context. Since it is clear that the authors have the data, at a minimum, they need to include some descriptive statistics about this excluded population, and the resulting overall statistics. Specifically, on Table 1 they report the number of antenatal and tocolytic hospitalizations for the study sample, and note that these are lower than what has been reported previously. This would be expected, given that they have excluded many of the cases most likely to need these hospitalizations. Thus, I think that they should report these rates for the excluded cases, and also for the entire population. This would make it much easier to understand the authors data and compare them with other countries. Related to this, I think that the authors should report the rates of prematurity and extreme prematurity (or low and very low birth weight). Given the potential for data problems with gestational age, LBW and VLBW may be the more useful numbers. This would be most useful if they reported this for the aggregate populations, and then separately for those who did and did not receive tocolysis. Another bit of information that would be useful would be to look at see how many of the cases with tocolytic therapy have a diagnosis of preterm labor. This should be 100%. Since there is some gray area in the diagnosis of preterm labor, this doesn’t mean the demand inducement isn’t occurring.
Response: We added statistics of the excluded cases in both Table 1 and Table 2 (page 16 and 17), as well as a few descriptions in the methods and results sections (page 7 and 10).

The information about prematurity, extreme prematurity, low birth weight (LBW), very low birth weight (VLBW) are not available in our dataset. The information is available in the Birth Registry in Taiwan but we are unable to link it with our dataset because all unique personal identifiers in our data were encrypted. We recognized this limitation in the discussion (page 10). All cases of tocolytic therapy have a diagnosis of preterm labor because we defined tocolytic hospitalization by ICD-9-CM codes 644.0 to 644.4 (diagnoses of preterm labor) listed in the diagnosis field (each case can have up to five diagnoses in the National Health Insurance Research Database).

2. Since they have the data, an interesting addition would be to look at the percentage of the tocolytic hospitalizations where glucocorticoids were also administered. In cases of preterm labor, for at least the first hospitalization, glucocorticoids should also be administered.

Response: The information about any tocolytic agents (e.g. glucocorticoids) used is unfortunately not available in our dataset, and we recognized this limitation in the discussion (page 11).

3. Something that isn’t clear and needs to be clarified is the difference between antenatal hospitalizations and tocolytic hospitalizations. I read the manuscript as if these were mutually exclusive, but I am not sure. If so, this seems a bit odd. If a women is admitted in preterm labor, standard therapy is to use tocolysis. Thus, I would think that there is a high degree of overlap in these hospitalizations. If I am wrong, and these hospitalizations do overlap, then the authors need to add information about the extent of overlap.

Response: Tocolytic hospitalizations are a subset of antenatal hospitalizations. We have clarified the difference between antenatal and tocolytic hospitalizations in the introduction and the methods section.

“Our analysis was focused on the use of tocolytic hospitalizations (ICD-9-CM codes from 644.0 to 644.4), which are a subset of antenatal
hospitalizations (ICD-9-CM codes from 640 to 676 with a fifth digit of “0” or “3”, or any diagnosis in combination with a code V22 [normal pregnancy] or V23 [high-risk pregnancy]).” (page 7)

4. I think that there are issues with selection bias in several of the authors control variables. For example, there is good evidence that high-risk deliveries have much better outcomes when they are transferred to a hospital with high-volume, tertiary-level, obstetric and neonatal services. Thus, one would expect that larger, higher level hospitals with have higher use of tocolytic therapy. This should be acknowledged in the discussion. I do not think that the authors need to address this in their analysis. If they want to look at it, distance to the provider, or differential distance between types of providers, is probably a good instrument.

Response: This is an excellent point and we have acknowledged this in the discussion (page 13).

“Also interesting are our findings that tocolytic hospitalizations were influenced by not only clinical factors but also physician and institutional conditions that had little relevance to clinical considerations. A possible explanation is that high-risk deliveries may have much better outcomes when they are transferred to a tertiary-level hospital with a high volume of obstetric and neonatal services [35]. Therefore, tertiary-level hospitals are likely to provide more tocolytic hospitalizations….”

5. One thing that would be an interesting addition, would be to compare the model the authors estimated with the same model, estimated on the excluded cases. Given the much higher risk profile of the excluded case, one would expect a higher rate of medical indication. Thus, my prior is that the parameter estimate for logger regional fertility rate would be smaller. This is just an interesting potential extension. I my opinion, this would make the manuscript more interesting. But, I don’t think that the authors should be required to undertake this extension.

Response: The definitions of antenatal/tocolytic hospitalization in previous research varied and there’s no consensus as to what an appropriate definition should be. We followed two prior studies (references 25 and 26) to determine our exclusion criteria, which included (see the footnote of Table 1, page 16): (1) women hospitalized for early pregnancy loss (ICD-9-CM 630-634 and 637-639) or elective termination (ICD-9-CM 635 and 636);
(2) women aged above 50 or below 15;
(3) women whose attending obstetrician/gynecologist’s age was below 25 or above 75;
(4) women with multiple deliveries;
(5) hypertension/eclampsia/pre-eclampsia (ICD-9-CM 642);
(6) excessive maternal bleeding/abrupted placenta/placenta previa (ICD-9-CM 762.0, 762.1, 762.2);
(7) premature rupture of membranes/incompetent cervix (ICD-9-CM 761);
(8) fetal distress (ICD-9-CM 656.3, 663.0, 768.3 and 768.4);
(9) maternal infection/chorioamnionitis (ICD-9-CM 762.7); and
(10) congenital abnormalities (ICD-9-CM 740-759).

These excluded cases may require different treatments other than tocolysis (e.g., termination of pregnancy or immediate c-section). We think modeling these cases and comparing with our results is beyond the scope of our manuscript because the excluded cases represent a mix of patients with many different medical conditions. For the reviewer’s information, we report the probit model on the excluded cases as follows:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probit model</th>
<th>Marginal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant term</td>
<td>-1.853 (0.408)**</td>
<td>6.358 (0.406)**</td>
</tr>
</tbody>
</table>

**Individual factors**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probit model</th>
<th>Marginal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.080 (0.001)**</td>
<td>0.012 (0.001)**</td>
</tr>
<tr>
<td>Wage</td>
<td>0.002 (0.0001)</td>
<td>-0.002 (0.002)</td>
</tr>
<tr>
<td>Having a major disease card</td>
<td>0.033 (0.007)**</td>
<td>0.111 (0.016)**</td>
</tr>
<tr>
<td>Having pregnancy-associated hospitalizations before</td>
<td>0.428 (0.006)**</td>
<td>0.067 (0.027)**</td>
</tr>
<tr>
<td>Previous year’s inpatient expenses</td>
<td>0.001 (0.0002)**</td>
<td>0.013 (0.002)**</td>
</tr>
</tbody>
</table>

**Institutional factors**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probit model</th>
<th>Marginal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed size</td>
<td>0.004 (0.001)**</td>
<td>0.001 (0.0006)**</td>
</tr>
<tr>
<td>Ownership</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>0.0436 (0.010)**</td>
<td>-0.020 (0.004)**</td>
</tr>
<tr>
<td>Private non-profit</td>
<td>-0.0002 (0.010)</td>
<td>-0.042 (0.004)**</td>
</tr>
<tr>
<td>Proprietary (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accreditation status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical center</td>
<td>0.497 (0.021)**</td>
<td>0.097 (0.03)**</td>
</tr>
<tr>
<td>Regional hospital</td>
<td>0.406 (0.017)**</td>
<td>0.082 (0.009)**</td>
</tr>
<tr>
<td></td>
<td>District hospital</td>
<td>Clinic (Reference)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>District hospital</strong></td>
<td>0.495 (0.014)**</td>
<td>0.043 (0.002)**</td>
</tr>
<tr>
<td><strong>Teaching status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching</td>
<td>0.094 (0.010)**</td>
<td>0.088 (0.010)**</td>
</tr>
<tr>
<td>Non-teaching (Reference)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physician factors**
- Male gender: -0.001 (0.010) 0.015 (0.011)
- Age: 0.003 (0.0005)** -0.001 (0.0005)**

**Area factor**
- Logged regional fertility rate: -0.329 (0.107)** -0.101 (0.042)**

<table>
<thead>
<tr>
<th></th>
<th>Observations</th>
<th>Log-likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>1,979,311</td>
<td>1,979,311</td>
</tr>
<tr>
<td>Log-likelihood</td>
<td>-196577.7</td>
<td></td>
</tr>
</tbody>
</table>

Robust standard errors are in parentheses. The three models also include a full set of time and regional dummies. *Statistically significant at the 10% level. **Statistically significant at the 5% level.

The marginal effect of fertility is smaller in the model with excluded cases, but is still significant. This result makes sense given the fact that the excluded cases contained many high-risk pregnancies.

Because the focus of our study is on the relationship between fertility decline and tocolytic hospitalization, we feel it is important to exclude in our study those high-risk pregnancies, including multiple deliveries, that would require more intensive antenatal treatments.

**Minor comments**

6. In the Introduction, I think that the authors should make clearer the issue about the effectiveness of tocolytic therapy. They do indicate that the evidence is mixed. This is probably a bit generous and some additional caution is probably warranted. But, they also need to add that there is no therapy that is proven to be effective at preventing preterm labor. Tocolysis is used because it is the therapy that has the best evidence to support any effectiveness at all. Given the very serious consequences of extremely preterm labor, it is almost universally agreed that it should be tried for cases <32 weeks gestation. As a related point, the evidence is much stronger that tocolysis can delay labor a little bit, and this is very valuable if this time is used to administer glucocorticoids and give them a chance to work, as there is very strong evidence that glucocorticoid therapy
speeds lung maturity and has very positive effects on many different neonatal outcomes.

Response: We have revised our introduction by citing more recent literature that shows conflicting evidence of tocolytic hospitalizations. The introductory paragraph now reads:

“Antenatal care generally improves maternal and infant health [1]. The most commonly stated reason for antenatal hospitalizations is having symptoms of threatened preterm labor [2-8]. Tocolytic treatment, which uses pharmacologic agents to inhibit uterine contractions and to prevent delivery before the completion of 37 weeks of gestation, is touted to reduce perinatal morbidity and mortality associated with threatened preterm labor [9,10]. However, the use of tocolytic hospitalization in antenatal care is controversial due to potential adverse health effects and conflicting evidence of effectiveness [8,11-15]. Research indicated that antenatal hospitalizations with a pregnancy-related diagnosis may impose significant economic and psychosocial burdens on pregnant women and their family and may increase costs for the health care system [3,13,16]. Several U.S. studies showed that tocolytic treatment accounts for one-quarter to nearly one-half of all antenatal hospitalizations [3,5-7,17]. Examining the conditions under which women receive tocolytic treatment, including factors unrelated to the woman’s clinical need, is necessary to understand whether the treatment are always justified.”

We do not discuss the use of tocolytic agents (e.g., glucocorticoids); neither do we speak to the issue of effectiveness, because it is not a focus of our study.

7. Methods. The authors do not mention that they did a full set of regression diagnostics. Given that Edward Norton was involved in the analysis, I am sure that these were conducted. They should just explicitly state that they have do so.

Response: We reported robust standard errors to fix the heteroskedasticity problem in the probit model (page 10 and Table 3).

8. Page 10, bottom. When the authors discuss the potential effects of IVF/ART, they should also note that these technologies are associated with a much higher
risk of multiples and other high-risk conditions.

Response: We have revised this sentence (page 12).