Reviewer's report

**Title:** Recurrence of perinatal death in Northern Tanzania: A registry based cohort study

**Version:** 2  **Date:** 31 March 2013

**Reviewer:** Regine Unkels

**Reviewer's report:**

Major compulsory revisions

**Abstract**

Background paragraph: Your results and discussion suggest that you aimed to estimate the risk of recurrent perinatal death and underlying factors.

**Methods**

Your results and discussion suggest that a case control study design would be more appropriate.

**Paragraph 2:** If I understand paragraph 4 correctly the data you collected prospectively were from 2008 to 2010 though in paragr. 2 you state you collected data prospectively from 2000 to 2010. If the follow-up period was at least 2 years for some and 6.6 years for others the data seem to be a mixture of retrospective and prospective data. This needs more elaboration. It might be useful to add a timeline here for better understanding.

**Paragraph 3:** It is not clear to me whether everything described here (interviews) is a routine part of the registry or belongs to the study design. I think it is important to describe the registry a bit more: Is it paper-based or computer-based, which data are entered. How are researchers alerted that a woman came back who already delivered and how did you make sure she gets the same ID. This will make later issues around limitations due to loss to follow-up clearer.

**Paragraph 4:** There is confusion over the definition of your cohort between this paragraph and figure 1. There is an exposed (865) and an unexposed cohort (18,936) from the text but a cohort of all 19,811 mothers who delivered in figure 1. I don’t think the latter is the correct definition. As well I think the difference in size of both cohorts is too big. As well a study cohort must be formed and completed before the beginning of a prospective study. The way you describe it some women had a shorter follow-up time than others.

**Paragraph 5:** You need to explain how you came to your sample size. As well I would assume there is a difference in risk of perinatal death in mothers with a
recurrence in the next pregnancy after the first death and in mothers who have a live baby in between. You included women with 2 – 4 subsequent pregnancies. I would assume this may make analysis more difficult and introduce a bias. For the same reason i find it difficult to define the first pregnancy of a study participant as the first pregnancy recorded in your data base. A woman who has delivered 3 live-born babies outside KCMC, then one stillborn baby in KCMC has a different risk of recurrence than a primipara with one stillborn in KCMC.

Results
It is very difficult to understand which group of women is referred to in the different paragraphs. I would advice to use subheadings to group your findings, e.g. according to your tables (general predictors, predictors in women with previous live birth, predictors in women with previous perinatal death.)

I would advice to add the analysis of recurrence risk per order of subsequent pregnancy (2nd, third, fourth subsequent pregnancy) as this may vary.

Paragraph 3: RR for all these conditions was higher than RR for perinatal death quoted in paragraph 2. But this finding is never assessed in the discussion although from what you write pre-eclampsia, low birth weight and prematurity in the first pregnancy seem to be more important predictors than perinatal death. All three may share the same underlying pathology with each other and with perinatal death, as well there is an increased recurrence risk for all three conditions on their own. It would be important to address this finding somewhere in the discussion.

Paragraph 4 and 5: Please refer to table 4 in the text. The findings you describe here are important but they are not addressed in the discussion. I recommend that you address the finding that a perinatal death of a term baby or with normal birth weight has this recurrence risk and that the RR is higher than for preterm babies or low birth weight.

Discussion
Your discussion focuses very much on risk factors for recurrence (exposure), however your study design is set around outcome (recurrence) as a variable of interest.

Paragraph 1: As this is the beginning of your discussion you should explain what you mean with the baby’s “condition” (You are talking about perinatal outcome at first delivery as a strong predictor for the outcome in a subsequent pregnancy, or about low birth weight or prematurity??). In the next phrase the risk needs to be defined (risk of what is 9%?). Next phrase: “If a previous baby was also born preterm or....(in addition to what? Do you mean to say that if a baby was dead and also preterm etc.)

Paragraph 5: An important limitation of this study is the fact that it is facility-based and the fact that KCMC is the biggest hospital can also introduce bias (who are the women who choose to deliver there)

Paragraph 5: The number of women included (24,443) and the time period (2002-2010) here do not match with the figures mentioned in the method section
and in figure 1.

Paragraph 6: According to the methods section women who were referred for medical reasons were excluded from the study and their data would thus not be available for a sub-study.

Conclusions

I think you cannot infer from women in Kilimanjaro Region to women in Africa. I would advise to make it less general and say women in Tanzania. The statement in your second phrase is valid for every setting in the world and this recommendation is already existing in Tanzanian National guidelines and WHO recommendations. Could you add here the findings from your study that were new or more important, e.g. the finding that especially women with normal term babies and perinatal death may have a high risk for recurrence? As well your recommendation should be more specific in terms of interventions needed. I agree that for the finding I’ve mentioned above, it is difficult to think of an intervention to avoid a recurrence here. To me your finding suggests that there are other factors contributing to these recurrences which we didn’t identify yet. So here, more research is needed. A disaggregation of data the stillbirth sub-set into fresh and macerated stillbirth might deliver a clue here. As well this finding may suggest problems in monitoring during delivery and this could be your argument. Underlying here may be a context-specific perception about perinatal death which prevents providers from seeing mothers with term and normal birth weight babies as at risk.

Discretionary revisions

Background

Research question not stated.

Paragraph 1: As your study is about facility-based perinatal mortality I recommend not to cite the results of community-based studies without mentioning that they will differ significantly from each other in terms of quantity and underlying factors.

Methods

I would advice to use sub-headings (e.g. birth registry at KCMC, sample size calculation, sampling method, data collection, data analysis).

Paragraph 4: Here you state that women who were referred for various medical reasons were excluded from the study initially but in discussion paragraph 5 you write about a sub-study after exclusion. That is not quite clear to me.

Paragraph 7: Could you explain why two statistical programmes were needed?

Results

Paragraph 3: Table 3 shows the recurrence risk, but what you write here is the perinatal mortality rate.

Paragraph 4: Please refer to table 4 for these findings in relation to perinatal death.
Discussion

Here as well I would advice to use sub-headings to group your discussion per “women with recurrence” and “women without recurrence”. This will inform your recommendations on what kind of additional interventions women with recurrent perinatal death should receive.

Paragraph 1: According to the research question in the abstract you aimed to estimate the risk of recurrent perinatal death. The “how” would be more appropriately clarified with a case-control design using recurrence as the outcome and the different risk factors would be the exposure.

Paragraph 2: At the end of this paragraph I would expect a discussion about possible reasons why the studies you quote report lower recurrence risks than yours.

Paragraph 3: Some readers might not be familiar with the concept of precurrence risk. Please add brief explanation.

Paragraph 4: It would be helpful to mention the background of the studies you quote.

Paragraph 4: The section about the probability of under ascertainment of perinatal death should be mentioned as well under limitations.

Paragraph 7: The assumption that assignment of a new hospital id is independent to outcome of the previous pregnancy might be wrong because some women in this setting tent to throw away their old medical records because they associate them with the loss. So if your system failed to find that she had already delivered at KCMC she may not volunteer this information either due to her experiences.

Paragraph 7: Not every reader (including myself) may be familiar with the concept of selective fertility. Could you briefly explain what it includes.

Conclusions

Paragraph 1: Women with no perinatal death in their first pregnancy cannot have a recurrent perinatal death in their second. I propose to re-phrase like this: “the risk of recurrence of perinatal death for women in Northern Tanzania...compared to a much lower risk for perinatal death for women with no history of perinatal death in their first pregnancy.”

Minor essential revisions

General comment: I would rather use the term delivery instead of birth throughout the text.

Abstract

Paragraph 1: f similar levels of relative risk of recurrence exist in Africa in addition to the much higher population risk, some women could carry an exceptionally high risk and might benefit from special prevention
strategies. We aim to estimate the facility-based recurrence risk of perinatal death in a low-resource setting.

Paragraph 3: The recurrence risk of perinatal death for women who already had lost one baby was
9.1% with a relative risk of 3.2 (95% CI: 2.2 - 4.7) compared to a much lower risk of 2.8% for women who had had a surviving child. Recurrence contributed 21.2% (31/146) of perinatal deaths in subsequent pregnancies. Preeclampsia, placental abruption, placenta previa, induced labor, preterm delivery and low birth weight in a previous delivery with a live child were also associated with increased perinatal mortality in the next pregnancy.

Paragraph 4: Some women in Tanzanian hospital settings who suffer a perinatal loss in one pregnancy are at a very high risk of losing their child in a subsequent pregnancy.

Background
Paragraph 1: In a facility-based study using data from Northern Tanzania, we found a perinatal mortality rate of 58 per 1000 live births [6]

Paragraph 3: If similar levels of relative risk of recurrence exist in African hospital settings against the much higher population risk, some women could carry an exceptionally high risk and might benefit from special prevention strategies.

Methods
Paragraph 2: Kilimanjaro region in Northern Tanzania and is one of four zonal referral hospitals in Tanzania. It receives deliveries from the local community as well as referred cases from distant areas.

Paragraph 3: Data from the medical records were abstracted and trained midwife nurses conducted interviews on a daily basis for every woman who delivered in the hospital using a standardized questionnaire. In addition, admitted mothers were asked to provide their antenatal care cards. Verbal consent was sought prior to the interview. All data were entered into a specially designed database system at the hospital.
Paragraph 4: After the exclusion of women who were referred to KCMC from rural areas for various medical reasons and those who had multiple pregnancies, a total of

We then formed a cohort of these women in the whole period of 2000 to 2010 and identified all subsequent births recorded in the registry.

Paragraph 6: Perinatal mortality was defined as a stillbirth of a baby of at least 500 grams or a recorded early neonatal end of phrase is missing.

Results

Paragraph 2: Table 3 shows that the perinatal mortality rate was 90.6 per 1000 births for recurrent perinatal loss compared with a perinatal mortality of 27.6 per 1000 births for those who had a surviving child in a previous pregnancy. This amounts to a 3.2-fold relative risk (95% CI: 2.2 - 4.7). Recurrence constituted 21.2% (31/146) of perinatal deaths in subsequent births.

Paragraph 3: Some other conditions during first pregnancy were independent predictors of perinatal mortality in the subsequent pregnancy for all women; these included preeclampsia (RR=4.5; 95% CI: 2.9 - 7.1), preterm delivery (RR=5.8; 95% CI: 4.1 - 8.0) and low birth weight (RR=6.5; 4.7 - 8.9).

For mothers who had delivered a baby at term or a normal birth weight baby, a perinatal death of the previous baby predicted a strong increase in the risk of perinatal death in a subsequent delivery.

Paragraph 4: Perinatal death at first delivery was a predictor for perinatal death at subsequent delivery, but the Strength of association prediction was also influenced by presence of other pregnancy complications (table 4).

Paragraph 6: If a woman had lost her first baby due to stillbirth, she had a 5.1-fold (95% CI: 3.2 - 8.1) risk of losing her next baby due to stillbirth, while her recurrence risk of losing the next baby in an early neonatal death was 2.2-fold (95% CI: 1.0-4.9) (Table 5).
Discussion

Paragraph 1: From our data from Northern Tanzania we have previously described the perinatal mortality and the distribution of causes of perinatal death [6]. In the current paper we describe how perinatal death in one pregnancy is associated with perinatal death in the subsequent pregnancies. For women who had lost a previous baby the risk of recurrent perinatal death was 9 per cent.

Paragraph 2: Although absolute risks were much higher than in western countries, the strength of association accorded to a 3.2-fold recurrence risk observed in our data was surprisingly consistent with associations observed in western countries [12-14]. Some studies have found slightly higher relative risks,[9, 15, 16] and one study in Afro-American women estimated a four-fold recurrence risk.[12] A 2-fold recurrence risk has been reported from Israel.[11]

When any of these conditions occurred in one pregnancy, the risk was high for a perinatal death in the subsequent pregnancy regardless whether the baby had died or not in the previous pregnancy.

Paragraph 4: Since 12 of the 32 who might have had subsequent births were lost in our follow-up, we may have lost 38% (12/32) of the women who had subsequent births in our follow-up of the cohort of 19 811 women.

Paragraph 7: A similar finding has been reported elsewhere.[13, 24] For our data this may be partly explained by selective fertility, or the tendency of families to compensate for the loss of a child. For our data, it is possible that women with a previous loss were more likely to show up at KCMC for a future delivery. This would bias estimation of selective fertility.

Paragraph 9: We estimated significant differences in the risk of perinatal death in a subsequent
deliveries depending on the outcome of a previous pregnancy. This opens the possibility that high-risk pregnant women in Tanzania or similar African settings may be identified and benefit from special clinical attention during their future pregnancies.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.