Author’s response to reviews

Title: Risk factors and outcome of patients with eclampsia at a tertiary hospital in Egypt

Authors:
Ahmad Mahran (ezzeldin_ahmad@yahoo.com)
Hashem Fares (hashemfares1976@yahoo.com)
Reham Elkhateeb (rehamelkhatreeb78@yahoo.com)
Mahmoud Ibrahim (hosnimahmoud60@yahoo.com)
Haitham Bahaa (haitham_bahaa@yahoo.com)
Ahmad Sanad (asasanad@hotmail.com)
Alaa Gamal (alaagamal316@gmail.com)
Mohamed Zeen El-Din (dr.muhamedzeen1980@gmail.com)
Eissa Khalifa (Eissa_mmk@yahoo.com)
Ahmed Abdelghany (Drahmed_abdlghany@yahoo.com)

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Author’s response to reviews:

Dear Mr. Boodhun,

Many thanks for revising our manuscript in consideration for publication in BMC Pregnancy and Childbirth. Our profound thanks go also to the reviewers for their valuable comments and suggestions. Please find below our responses to the points raised by the reviewers. We have uploaded a revised version of the manuscript including the necessary corrections. The changes in the manuscript have been highlighted with a yellow background.

Reviewer 1:

First, we would like to thank you for your positive comments and important points you aroused that would hopefully improve the manuscript and make it more suitable for publication.

1. There draft does not contain an abstract or include page numbers.
Abstract and page numbers were added.

2. Inclusion criteria - how did the authors define a "reliable history" of fits at home? It might be better to replace “fits” with seizures.

Fits was replaced by seizures.

3. The methods section focuses on how data were obtained for women with eclampsia, but provides no information on how data were obtained for women who did not have preeclampsia. This information is important, as data from women who did not develop eclampsia are used in the analysis of risk predictors. Were women who were excluded from the eclampsia group due to epilepsy, etc. included in the "all deliveries" group?

This is an important comment. Actually, data from women who did not have preeclampsia were obtained from patients' files at the hospital. Patients who were excluded due to epilepsy were included in the all deliveries group. A clarification was added to the methods section.

4. In the first paragraph of the discussion, the authors note that they observed an incidence of eclampsia of 1.2%. The value that they have calculated is not an incidence; it is the percentage of patients delivering at the hospital where the study was conducted who had eclampsia. To calculate the incidence or prevalence, the authors would need to exclude all women (with and without eclampsia) who delivered at the study hospital but lived outside of the hospital catchment area. They would also need to provide evidence that their hospital performs all or almost all of the deliveries in that catchment area. The incidence of eclampsia in the population may differ from the percentage of patients with eclampsia at the study hospital for several reasons. For example, the authors may have observed higher rates of eclampsia than would be expected in the general population due to 2 factors:

- Referral bias: The methods section notes that this is a tertiary care referral hospital and that women from outside the hospital catchment area who develop eclampsia are likely to be referred to the study hospital by health care providers, regional/local clinics, and patient self-referral. This would lead to a higher proportion of patients with preeclampsia when compared to other hospitals and clinics in the area that don't receive patients referred for severe complications.

- Deliveries at other centers: If healthy/low-risk pregnant women in the hospital catchment area routinely deliver at other clinics, this would also lead to higher rates of eclampsia at the study hospital compared to other hospitals or clinics. The authors would be underestimating the percentage of healthy deliveries and overestimating the percentage of women who develop eclampsia.

This is really a very important comment. The incidence was changed to percentage of patients delivered at the hospital. Actually, there will be a referral bias as many of the patients with eclampsia in this study were referred from other hospitals or clinics outside the hospital.
catchment area. Also, most of the low risk pregnant women at the hospital catchment area give birth at other clinics or smaller hospitals. We agree with you that the term percentage is more accurate.

5. Table 1 is quite confusing, as it blends a standard demographics table describing the study sample with outcome data on risk factors. Table 1 should just describe the demographics for the study sample, using 4 columns (all deliveries, eclampsia, no eclampsia, p value for a single test indicating whether the groups are different). Risk predictors should be identified using a multivariate model, instead of by calculating odds ratios for one variable at a time. This would allow the authors to identify confounding variables and determine which things are risk factors after adjusting for confounding. The results of this multivariate analysis should be presented in the text or in a separate table.

Thank you very much for this valuable comment. Actually, there was some confusion that was sorted with the statistician. The multivariate analysis was already done so the adjusted odds ratios were presented. Table 1 was modified to include: all deliveries, eclampsia, no eclampsia and P value. Table 2 was added to present the adjusted odds ratio for each risk factor. The statistical methodology section was also corrected.

6. The discussion of risk predictors is rather confusing. The authors focus on the percentage of women with eclampsia who have particular characteristics (i.e. BMI > 25 kg/m2). This percentage by itself is not very meaningful. For example, 42% of eclamptics being <20 years old is not very important if 42% of non-eclamptics are <20 years old, but is much more important if only 17% of non-eclamptic women are <20 years old. As described above, multivariate analyses are needed to determine which things are risk predictors after adjusting for confounding. The risk predictors section of the discussion should focus on the results of this multivariate analysis.

As mentioned in reply for the comment no.5s. Multivariate analysis was performed so the effect each risk factor was assessed independent from other confounding factors. The discussion section was corrected accordingly with focus on the adjusted odds ratio for the most important risk factor.

7. The discussion needs to acknowledge the limitations of this study, in particular referral bias (implications for the percentage of patients who developed preeclampsia were discussed above; in addition, the referral of complex cases may mean that women with eclampsia have more severe symptoms and/or worse outcomes that would be expected at other centers in the region). Points of strength and limitations were added to the discussion section.

8. In table 6, reporting birth weight centile would be more meaningful that reporting birth weight. This would account for the range of gestational ages at delivery. Birth weight was replaced with birth weight centiles.
9. Page 6 line 7: there appears to be an extra 0 - "The annual number of deliveries at this tertiary hospital ranges from 10,000 to 12,0000."

Thank you for the meticulous observation. The figure was corrected.

Reviewer 2:

First, we would like to thank you for your positive comments and valuable questions. We hope that addressing these issues would hopefully improve the manuscript and make more suitable for publication.

* Is the risk associated with short duration of marriage independent of the age of the patients?

As multivariate analysis has been performed, each risk factor is assessed independently without the effect of other confounders and adjusted odds ratio is calculated.

* Is malaria endemic to this region of Egypt? Is the observed association with anemia associated with malaria?

Malaria is not endemic in Egypt and there is no association between malaria and the association observed with anemia. The association between anemia and preclampsia / eclampsia may be due to the associated micronutrients and antioxidants deficiency. This possible explanation was added in the discussion section.

* Is the association with interval between marriage independent of the risk associated with advancing maternal age?

As mentioned in reply for the first comment, each risk factor is assessed independently without the effect of other confounders and adjusted odds ratio is calculated.

* Is MgSO4 used for primary prevention of eclampsia? (MAGPIE) What percent of the eclamptic cases had seizures after presentation to the hospital with hypertension and were therefore eligible for primary prevention? Only 16.8% presented having already had a seizure.

We strongly believe in the role of MgSO4 in prevention of fits. However, this is another point related to our limited resources as in many occasions, MgSO4 was not available at the hospital and there was lag of time till it could be made available and be given to patients presented with severe preeclampsia. As a result, many patients have seizures during this time lag. In addition, we do not have sufficient data about whether the proper dose was given after delivery. We have high work load at the hospital and relatively insufficient nursing staff, so improper dosing or early discontinuation of treatment are likely.

* Can the authors conclude that the use of cesarean section contributed to complications? The reported rate is not higher than other reports. C-section is frequently done for fetal indication or for the acuity of maternal illness.
We agree with you that this conclusion cannot be made from our study. We highlighted the need for further studies to assess the effect of the mode of delivery in cases of severe preeclampsia/eclampsia on the maternal and perinatal outcome.

* In Table 1, 1-3 prenatal visits has an OR of 1.29 (1.18-1.39) but with a p-value of <0.534. Is this a typo?

Apologies for this typing mistake. It was corrected in the table.

* The authors report aOR's and indicate that a logistic regression was performed. Unadjusted OR's should be included. In addition, more details of the regression analysis should be included. Given the number of potentially interrelated variables, should a multivariate mode; be used?

Thank you for this crucial point you aroused. We revised this point with the statistician. Actually, the multivariate analysis was performed to allow assessment the effect of each risk factor on the outcome independent from other confounding factors so, the adjusted OR is displayed in the results. That was corrected in the statistical methodology section.

* Some information about oral antihypertensive dosing would be helpful. If dosing was fairly nominal, a more aggressive oral dosing regimen might improve outcomes.

Actually, no enough data was available regarding the doses of antihypertensive therapy given. It is also obvious that not all patients had oral antihypertensive therapy. It is a good point for further research to assess the influence of more aggressive antihypertensive therapy on the outcome in severe preeclampsia/eclampsia.

The study suggests a number of interventions that might decrease the eclampsia rate. Some are deeply rooted in social conditions and likely interrelated, (age, education, duration of marriage < length of gestation, obesity). These are difficult to address but overtime could be amenable to public health intervention. Inadequate prenatal care is likely related to social factors but could be addressed independently. It is important to note that >8 visits had a lower risk than even 4-8 visits despite some recommendations for a reduced intensity of prenatal care. (This may of course not be causally related.) It seems that 83% of the patients presented prior to having a seizure. If we are to believe the MAGPIE Trial, 104 cases of eclampsia (half of the 208 without a presenting seizure and presumably hypertensive) could have been prevented with MgSO4. This if course leaves the question of how many women would need to be treated for primary prevention to achieve this outcome. Can the authors address this question?

In this study, we tried to draw the attention to the government and the ministry of health to the main risk factors associated with eclampsia. We hope the results of this study will help to implement policies which might reduce these risks through public education which prove effectiveness in our community in management of other health problems like endemic infections as Schistomiasis. Regarding, the role of antenatal visits, we believe it is not only the number of visits, but also the quality of care provided. We need to ensure that blood pressure measurement and urine test for albumin are done every visit. Our explanation for the large number of patients developed seizures after admission to the hospital was detailed in reply to comment no.4. It is
another problem related to the limited resources and lack of fund. These points were clarified in the discussion section in the new version of the manuscript.

We hope that these responses would be satisfactory to the reviewers and the editorial team. We are happy to respond to any other comments from the experts.

I look forward to your response

Kind regards.

Yours sincerely,

Ahmad Mahran (corresponding author).