**PEER REVIEW HISTORY**

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**ARTICLE DETAILS**

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Clinical features of isolated gestational proteinuria progressing to pre-eclampsia: retrospective observational study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Akaishi, Rina; Yamada, Takahiro; Morikawa, Mamoru; Nishida, Ryutaro; Minakami, Hisanori</td>
</tr>
</tbody>
</table>

**VERSION 1 - REVIEW**

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Shigeki Matsubara</th>
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<tbody>
<tr>
<td></td>
<td>Jichi Medical University, Japan</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>25-Feb-2014</td>
</tr>
</tbody>
</table>

| GENERAL COMMENTS     | I have minor concerns that may be added or corrected, which I described in "to Author section". These are quite a trivial matter and thus I marked "accept" regardless of these two comments. I want to leave it to Editor's discretion how to treat this point. Thank you for giving me a chance to look at this interesting manuscript. Since “proteinuria only” has been excluded from the definition of preeclampsia, many obstetricians, including me, concerned about that “protein only” is only one (transient) phase before full manifestation of preeclampsia and this type (the authors called it as P-PE) may show even worse outcome compared with other type of PE. In a sense, this "concern" has been proved true; the manuscript clearly indicated this. I have only two minor concerns. 1. In abstract, the last statement: I guess that the conclusion may better be toned down. The authors studied only 10 patients and thus whether P-PE is "more severe" is not yet completely determined. I guess that the following may illustrate the situation better; ", thus suggesting that P-PE women may constitute a more severe form of PE than O-PE." You need not use the phrase per se. In fact, the authors stated the same thing at line 2-3 of page 10. 2. P-PE had shorter length of gestation. This means that P-PE deteriorated earlier than O-PE. The context is clear. However, since termination is "intentionally done", i. e., "indicated preterm delivery" is chosen, "when delivery occurs" depends solely on the judgment of the attending doctors. I do not want the enlargement of the volume; the present manuscript is of the upper limit of the volume. So, you may not have a space to describe the “indication” criteria of the pregnancy termination. But, I wish to state the following meaning in the text very briefly; "Although the date of delivery was decided according to the maternal and fetal condition, and thus, “arbitrarily” (or based on the judgment of the attending doctors), we employed the same criteria for pregnancy termination to both P-PE and O-PE, and thus “earlier delivery” in P-PE reflects worse maternal-fetal condition in P-PE." You need not use the expression per se. I want you to touch the things to make the situation more correct. |


Atsuo Itakura  
Juntendo University, Japan

14-Mar-2014

Dr. Rina Akaishi et al. conducted a retrospective case-control study (bmjopen-2014-004870) regarding the timing of proteinuria emergence in preeclampsia. They concluded P-PE constituting a more severe form than O-PE. This paper continues investigations by this group. The article is well referenced, and data are clearly presented. The authors discussed their study limitations as well as generalization of the study and biases. NICE guideline (CG107) 10) does not refer the timing of proteinuria emergence, nor recommend repeat quantification of proteinuria after diagnosis of preeclampsia. This paper deals with an important issue about management of PE.

This reviewer should address several concerns.

1. Their conclusion that constituting a more severe form of PE than O-PE is not well supported by the data. The severity of PE should be evaluated from clinical point of view. Comparison of neonatal and maternal outcome may support this.

2. They compared the length of pregnancy among these groups. What was the cause of preterm birth? The statement of your standard to offer birth before 37 weeks may be helpful for understanding.

3. It is hard to understand their motivation and aim of this study. The authors had better state them clearly in Introduction.

4. The Discussion section seems too lengthy. The review of previous works is not essential, and could be shortened by 50%. The clinical implications of the study should be emphasized more.

Reviewer: 1  
Reviewer Name Shigeki Matsubara  
Institution and Country Jichi Medical University, Japan

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1. In abstract, the last statement: I guess that the conclusion may better be toned down. The authors studied only 10 patients and thus whether P-PE is “more severe” is not yet completely determined. I guess that the following may illustrate the situation better; “, thus suggesting that P-PE women may constitute a more severe form of PE than O-PE.” You need not use the phrase per se. In fact, the
authors stated the same thing at line 2-3 of page 10.
Reply: We revised it to “thus suggesting that P-PE women may constitute a more severe form of PE than O-PE women do.”

2. P-PE had shorter length of gestation. This means that P-PE deteriorated earlier than O-PE. The context is clear. However, since termination is “intentionally done”, i.e., “indicated preterm delivery” is chosen, “when delivery occurs” depends solely on the judgment of the attending doctors. I do not want the enlargement of the volume; the present manuscript is of the upper limit of the volume. So, you may not have a space to describe the “indication” criteria of the pregnancy termination. But, I wish to state the following meaning in the text very briefly; “Although the date of delivery was decided according to the maternal and fetal condition, and thus, “arbitrarily” (or based on the judgment of the attending doctors), we employed the same criteria for pregnancy termination to both P-PE and O-PE, and thus “earlier delivery” in P-PE reflects worse maternal-fetal condition in P-PE.” You need not use the expression per se. I want you to touch the things to make the situation more correct.
Reply: We added “Indication for an early delivery in PE women” to the Materials and Methods.

Reviewer: 2
Reviewer Name Atsuo Itakura
Institution and Country Juntendo University, Japan
Please state any competing interests or state ‘None declared’: None declared
Reply: We stated that “None of the authors have any conflict of interest.” before Reference list.

Thank you very much for the opportunity to review this paper (bmjopen-2014-004870). Dr. Rina Akaishi et al. conducted a retrospective case-control study regarding the timing of proteinuria emergence in preeclampsia. They concluded P-PE constituting a more severe form than O-PE. This paper continues investigations by this group. As the authors stated, these findings may have been distorted by incidental bias due to the small size of the study population. And their conclusions may overreach the extent of the information provided by the data. This study seems having a lower priority in comparison with their previous one.

Dr. Rina Akaishi et al. conducted a retrospective case-control study (bmjopen-2014-004870) regarding the timing of proteinuria emergence in preeclampsia. They concluded P-PE constituting a more severe form than O-PE. This paper continues investigations by this group. The article is well referenced, and data are clearly presented. The authors discussed their study limitations as well as generalization of the study and biases.
NICE guideline (CG107) 10) does not refer the timing of proteinuria emergence, nor recommend repeat quantification of proteinuria after diagnosis of preeclampsia. This paper deals with an important issue about management of PE.

This reviewer should address several concerns.
1. Their conclusion that constituting a more severe form of PE than O-PE is not well supported by the data. The severity of PE should be evaluated from clinical point of view. Comparison of neonatal and maternal outcome may support this.
Reply: We agree with Prof. Itakura’s opinion partly. However, as stated in the beginning of the Conclusion of Abstract, we stated it with respect to amount of protein loss in the urine, size of edema, and degree of enhanced coagulation-fibrinolysis.

2. They compared the length of pregnancy among these groups. What was the cause of preterm birth? The statement of your standard to offer birth before 37 weeks may be helpful for understanding.
Reply: We added “Indication for an early delivery in PE women” to the Materials and Methods.

3. It is hard to understand their motivation and aim of this study. The authors had better state them clearly in Introduction.

Reply: As already mentioned in the Introduction, proteinuria-preceding PE is only recently acknowledged as a subtype of PE. In addition, it is emphasized only recently to monitor blood variables in the management of PE women. Therefore, there have been scarce reports regarding clinical and laboratory features of proteinuria-preceding PE. We tried to characterize well the clinical and laboratory features of proteinuria-preceding PE in this study. This is stated in the end of the Introduction of the original manuscript.

4. The Discussion section seems too lengthy. The review of previous works is not essential, and could be shortened by 50%. The clinical implications of the study should be emphasized more.

Reply: We tried to reduce words count of the Discussion. However, we were able to do it only by 10% from 1262 in the original version to 1144 in the revised version. As we dealt with relatively new 3 topics including proteinuria-preceding preeclampsia, the method (protein-to-creatinine ratio) for the assessment of proteinuria in pregnant women, and weight gain in preeclampsia women, we considered that sufficient discussion is needed for readers to understand better this work. The clinical implication is already stated in the end of the Discussion as that “All of these results suggested that pre-eclamptic women with IGP followed by hypertension constitute a more severe pre-eclampsia group.” We wanted to discuss about treatment for IGP women as the clinical implication. However, it is unknown at present how to treat women with 1+ test result on dipstick in the absence of hypertension, because the dipstick testing has a high false positive rate. Therefore, we hesitated to refer deeply to clinical implication.

We omitted following two parts in blue of the original Discussion.
1. “increased likelihood of developing PE[12].: among 755 normotensive women, 14% of the 50 women with positive dipstick test results in two successive antenatal visits later developed PE, while 2.0% of 705 women without such characteristics developed PE. Therefore, it is apparent that some PE women develop proteinuria first in the absence of hypertension.”
2. “considered as an important clinical sign equal to hypertension., although how many women with IGP or GH progress to PE was not determined in this study. To our knowledge, there have been two previous reports regarding the number of women who develop PE after showing GH or IGP[5, 9]: 15% – 26% women with GH progressed to PE,[5, 9] while approximately 50% of women with IGP progressed to PE,[5] suggesting that IGP rather than GH is a stronger risk factor for PE.”
Clinical features of isolated gestational proteinuria progressing to pre-eclampsia: retrospective observational study

Rina Akaishi, Takahiro Yamada, Mamoru Morikawa, Ryutaro Nishida and Hisanori Minakami

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