ANSWERING REVIEWERS

Aril 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10240-review.doc).

Title: Preeclampsia from a renal point of view

Author: Janina Müller-Deile and Mario Schiffer

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The manuscript has been improved according to the suggestions of reviewers:

- Format has been updated
- Revision has been made according to the suggestions of the reviewer. Please remark our point by point response below:

Reviewer *00742261*

1) It is right that obstetricians are not among the authors. That is why our review is entitled "preeclampsia from a renal side of view". As nephrologists it was our purpose to review the pathophysiology, animal models, biomarkers and therapy options for preeclampsia with a main focus on the kidney. As suggested by the reviewer we moderated our introduction by writing that we are likely the first authors to review preeclampsia in this constellation at least from the nephrologists' side of view.

2) To our mind the best method to determine the GFR in pregnancy is the mean of urea clearance and creatinine clearance obtained from collected urine. We thank the reviewer for his advice to be more precise in this point.

3) Regarding proteinuria in preeclampisa our review discusses the different methods to measure proteinuria. We stated that 24-hour urine collection is the gold standard for proteinuria and discussed UPC ratio with its known advantages and disadvantages. Relating to cut-off values for UPC ratio we already mentioned that UPC ratio cannot rule out preeclampsia completely and give reference for this.

Nevertheless, we suggest using UPC ratio as first screening tool for preeclampsia because of its high sensitivity (ref 15). We discussed this further in the conclusions of the second version of our review to be more comprehensive. To address the reviewers' comments we included more studies with UPC ratio as a diagnostic tool in preeclampsia (ref 14-16).

4) The reviewer is right that recently eadema is not included in the definition of preeclampisa. As suggested we included the article of *Gifford et al* where preeclampsia is defined as the combination of pregnancy induced hypertension and proteinuria (ref 22).

5) The reviewer repeated that the current definition of preeclampsia involves the presence of proteinuria and thus proteinuria cannot be absent in preeclampsia.
Fact is that the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for diagnosis of preeclampsia in 2013 (ref 23).
Therefore, it is possible that in recent studies 10 % of women with clinical and/or histological manifestations of preeclampsia had no proteinuria (ref 24). We hope that the definition of the American College of Obstetricians and Gynecologists is sufficient to convince the reviewer that proteinuria is not a necessary demand for defining preeclampsia.

6) We agree that the incidence of postpartum preeclampsia is dependent on the population included in the study. The incidence of preeclampsia in the postpartum period was 5.7% in a 10-year retrospective case series (42). In the same analysis 15.9% of hypertensive or preeclamptic women in the postpartum period develop eclampsia.

7) The reviewer is completely right that uric acid is a well-known parameter in management of preeclampsia. Therefore we discussed this biomarker more in detail (see page 11, 12).

8) Table 1 is modified from *Gifford et al*. We declared that in the revised version of our review.

9) Figure 1 is our own one.

10) Regarding to ourt treatment section vaginal or cesarean birth depends on several factors, such as the position of the baby, the dilation of the cervix and the baby's condition. Therefore we do not give a concrete recommendation on this even though in most situations vaginal delivery is possible.

11) As our review should focus on renal aspects of preeclampsia we removed the passage about acceleration of lung from of our review.

129 In the end of our manuscript we give our own conclusions about the aspects reviewed. Random UPC ratio is helpful primarily when it is below 150 mg/g because then 24-hour proteinuria of more than 300 mg is unlikely. The accuracy of this UPC ratio in predicting proteinuria >300 mg in 24-hour urine collection in pregnant women with suspected preeclampsia had a sensitivity ranged from 90-99% and specificity ranged from 33-65% (ref 15). With this high sensitivity UPC ratio is suitable as a screening parameter. Screening tests do not need high specificity because they have to be confirmed by a second test that would be 24-hour urine collection in this case. In pregnancies where others signs of preeclampsia are already present 24-hour urine collection should be done at first.

Reviewer *00742373*

1) Reviewer 00742373 is totally right that plasmapheresis was only done in a few cases of preeclampsia so far. Nonetheless, it was promising in otherwise therapy refractory cases. There is no animal model for plasmapheresis at the meantime. Therefore the only way to get more experience on this field is the clinical use in selected patients. We want to clarify that plasmapheresis definitely is not a common treatment strategy in preeclampsia but could be an option for otherwise therapy refractory cases. We attenuated our statement about plasmapheresis in the way that we would only recommend it in specialized centers with first class experience on the filed and with written consent of the patient after detailed education about the risks and experimental status of this therapy.

2) As preeclampsia is characterized by a reduction in circulating plasma volume diuretics are not generally recommended in preeclampsia. There are significant warnings against the use of thiazides during pregnancy that mention metabolic risks to the mother and fetus including hyponatremia, hypokalemia, thrombocytopenia, hyperglycemia. In our review we do not recommend diuretics unless pulmonary edema has developed. We want to point out that diuretics should only be used in live threatening condition as pulmonary oedema or brain oedema. Again, there are no recommendations for dating, dosage or time for diuretics in this situation as it would be an individual symptom dependent and symptom guided therapy in life threatening oedema. We recommend to get written approval for the use of diuretics from the patient concerned after detailed

education on risks and side effects during pregnancy. Measures to respond to blood pressure drops must always be available and vital signs of the mother and foetus must be controlled continuously under diuretic treatment. This includes continuous electronic foetal heart rate monitoring and cardiovascular monitoring of the mother.

Reviewer 00729478

no changes required

Reviewer 00397616

no changes required

- References and typesetting were corrected

We hope that the reviewers acknowledge our changes and we would like to submit the revision of our review. Thank you again for publishing our manuscript in the *World Journal of Nephrology*

Sincerely yours,

Janina Müller-Deile

Corresponding authors:

Janina Müller Deile, M.D. and Mario Schiffer, M.D.,

Division of Nephrology, Hannover Medical School, Carl-Neuberg-Str. 1

30625 Hannover, Germany

Phone++495115324708

FAX++49511552366

e-mail: schiffer.mario@mh-hannover.de