Reviewer’s report

Title: Oxidative stress and endothelial function in normal pregnancy versus pre-eclampsia, a combined longitudinal and case control study. The Endopreg study.

Version: 1 Date: 02 May 2017

Reviewer: Tracey Weissgerber

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The manuscript describes the protocol for the Endopreg Study, which measures oxidative stress and endothelial function longitudinally during pregnancy, and at the time of delivery and postpartum in women with normal vs. complicated pregnancies (preeclampsia, IUGR, PIH, preterm birth). This study has the potential to provide interesting data on the time course of changes in oxidative stress and endothelial function in normal pregnancies, and at delivery and postpartum in complicated pregnancies. However, there are some points that require clarification.

The description of "angiogenic or placental PE, formerly called early onset" and "non-angiogenic or maternal PE, formerly called late onset" oversimplifies and overstates existing findings. While many women with early onset PE have abnormal concentrations of angiogenic markers, there are also women with preeclampsia at term who have abnormalities in angiogenic markers. These women do not fit into the authors classification scheme. There are also women who develop early onset preeclampsia AND have significant maternal risk factors, including underlying cardiovascular or renal disease, hypertension, diabetes, etc. The field is currently focused on identifying and learning to recognize different subtypes of preeclampsia (1,2); yet the authors present this as fait accompli. Are the authors confident that if a women with preeclampsia has normal concentrations of sFlt-1 and PlGF, we can conclusively say that the placenta is completely normal? Or that there are only two types of PE? A more balanced approach would be to state that both maternal and placental factors contribute to PE and the relative contributions of each likely vary from woman to woman. Researchers are currently working to identify different subtypes of preeclampsia, and classifications based on both clinical presentation (i.e. early vs. late onset; mild vs. severe) and pathophysiologic processes (i.e. maternal vs. placental, angiogenic vs. non-angiogenic) have been proposed. Women with early onset PE are more likely to have abnormalities in pro-and anti-angiogenic markers, compared to women with late onset PE.

The paragraph on offspring effects of a PE pregnancy seems out of place, as the protocol does not study offspring.

For PE, preventive interventions such as aspirin are only recommended for high-risk women. This should be clarified. Furthermore, that protocol rationale depends on the assumption that these interventions will also be effective in women who would not be identified as high risk by current algorithms, but will be at risk based on elevated oxidative stress and endothelial function in the first trimester. This should be explicitly stated. Finally, the authors should consider the possibility that by looking for women who have abnormalities at 12 weeks, they may be
targeting a subset of women predisposed to early onset PE or to specific pathophysiologic pathways (i.e. pre-existing maternal vascular dysfunction). The authors should have a plan for identifying/evaluating possible subgroups of PE patients in their analysis.

The study hypotheses appear out of order. For example, "oxidative stress and endothelial function can be measured" follows two aims based on findings RE: endothelial function and oxidative stress. Also, if we don't already have sufficient information to confirm that the measurements that the authors are using are effective, why are these measurements being performed? What gold standard are the authors comparing their results with to confirm that this aim is successful?

There is nothing in the protocol that tests aim 4 (oxidative stress and endothelial function can be improved by interventions…)

I could not find an analysis plan for aim 5 (preeclampsia prediction).

Note that the definition of PE as written does not clearly require a sustained elevation in blood pressure. Do the authors require multiple elevated BP measurements?

For early and late PE, please clarify whether <34 weeks refers to the gestational age of PE diagnosis or of delivery.

Will FMD measurements include assessment of the shear stimulus, as recommended by guidelines (3)? Will LFMC be measured (4)?

For all measurements, will the person completing the measurement or be blinded to study group?

The case-control study includes 44 women/group (control, preeclampsia, PIH, pre-term birth, IUGR), where women with complications will be matched to controls for maternal and gestational age, parity, smoking behavior and ethnic group. In order to do this, the authors would have to carefully select women in each pregnancy complication group to ensure matching - this could lead to biased selection of women with complications. For example, the study includes a pre-term birth group; therefore matching for gestational age will require all other women in the study to complete testing prior to term. Women who develop PE, PIH or IUGR at term could not be enrolled. Even matching each group separately to the control group would be impossible, given that the control group includes the same number of women as the other groups. Adjusting for potential confounding variables in the analysis would be a better approach.

The rationale for the study is heavily focused on identifying nulliparous women at risk for pregnancy complications; however the study is not restricted to nulliparous women.

References


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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