Reviewer’s report

Title: First Trimester PAPP-A Levels Correlate with sFlt-1 Levels Longitudinally in Pregnant Women with and without Preeclampsia

Version: 1 Date: 4 December 2012

Reviewer: Asma khalil

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Major Compulsory Revisions

1. Methods section: the authors should define how they selected these cases (from all those who fulfilled the inclusion criteria). This is an important point to determine whether this is a cohort or case-control study. The authors commented on the incidence of PE in their study, which implies a cohort study. If this is the case, the authors should describe the study population in detail, including those lost to follow-up and other pregnancy outcomes such as pregnancy induced hypertension. If this is a case-control study, the authors should not calculate the incidence of PE.

2. Methods section: the authors should comment on the storage duration of the samples, and whether these samples were previously thawed and re-frozen. This is important, particularly as some of the study results contradict what is already published.

3. I find it difficult to understand why the authors, or readers, might be interested in the correlation between PAPP-A levels in the first trimester and the levels of the angiogenic factors in the second and third trimesters. The authors should justify the need for, or value of, this study. Why did they not measure PAPP-A in the other samples too? What is the clinical significance of this study?

4. Did the authors conduct a power calculation? If so, please include it in the Methods section, particularly as many of the results were not statistically significant.

Minor Essential Revisions

1. Tables: please state the actual p values instead of ‘NS’.

2. There are some minor mistakes such as Page 11, line 252: “associated with”, the word “with” is missing.

Discretionary Revisions

1. The manuscript is well written. However it lacks clinical relevance; perhaps the authors could suggest some.

2. Some of the sFlt-1 results, in particular those in the first trimester, are
unexpected and contradict other studies. s-Flt has been reported, by the same authors and others, to be elevated in pre-eclampsia, even before the development of the clinical picture. However the levels are not significantly higher in the first trimester. So the fact that the authors report that it is significantly lower is unexpected, but might be interesting! The authors commented on this in the Discussion. However it is unlikely that the small difference in the gestational age explain this difference. Could they suggest any other possible explanation?

3. The results of PIGF in the first trimester are also unexpected. You would expect that the levels would be lower (even if not significant), even if the cases of pre-clampsia included in this study are mainly late-onset. It is surprising that the levels are higher. The authors should elaborate on the possible mechanisms.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests