Reviewer's report

Title: Hypertension after preeclampsia in relation to the C1114G polymorphism (rs4606) in RGS2: data from the Norwegian HUNT2 study

Version: 1 Date: 3 January 2014

Reviewer: Bjørn Egil Vikse

Reviewer's report:

The study submitted by Kvehaugen et al is interesting and focuses on an important association between preeclampsia and later hypertension that previously has been investigated in depth only in few studies. Especially interesting is the aim to investigate how the different factors preeclampsia and rs4606 polymorphisms affect later risk of hypertension. The main strengths are the population-based design and the high number of subjects in subgroups, as well as the very good research question that is described in the introduction.

Major compulsory revisions

1. My main concern is that the statistical analyses are presented in a somewhat disorganized manner and may have been overinterpreted. My comments 2-4 go in more depth on this comment.

2. The authors use several different endpoints (systolic blood pressure above 140/160 and/or use of antihypertensive medications or blood pressure above 140/90 or 160/100 and/or use of antihypertensive medications). The paper would benefit from a clearer strategy on what endpoint that actually was used in the abstract, in tables and in the conclusion.

3. The findings in Table 2 that the rs4606 polymorphisms neither were associated with later hypertension in the control nor in the preeclamptic women, leave me wondering whether the findings in Table 3 are based on large enough numbers of women or whether these findings are mainly coincidental. Supporting my skepticism is the impression that the endpoint used in Table 3 was one third as common as the endpoint in Table 2 (based on numbers reported in Table 1 for number of subjects with systolic blood pressure above 160 vs 140 mmHg). When results for Table 2 were presented, low numbers in subgroups were used as a reason for not finding statistical significance. Adjusted analyses in general demand larger numbers in subgroups, the results in Table 3 are however based on smaller numbers. For the main results in Table 3, the authors should present number of subjects in subgroups (for example how many women with preeclampsia had hypertension and the different genotypes) and unadjusted results (or minimally adjusted for current age only) should be presented before the adjusted results. An argument for minimally adjusted analyses with adjustments for current age (and possibly also BMI) could be made, as these variables are clear confounders of any association with hypertension. I appreciate the authors' argument on lines 302-304 on top of page 14 for the multivariate analysis with preeclampsia and genotype in the same model as the
main analysis, but unadjusted (or minimally adjusted analyses) should also be presented in tables.

4. The authors have chosen to focus on severe hypertension (defined as systolic blood pressure >160 and/or use of antihypertensive medications) in the abstract and conclusions. The negative findings for the normal definition of hypertension (blood pressure >140/90 and/or use of antihypertensive medications) are more briefly commented upon. In my opinion, the authors should focus on the results for the normal definition of hypertension and that these results should be presented in a table similar to Table 3 (but including N's). I appreciate the thorough description in the results text, but these results should be presented in a table. Results for severe hypertension should be presented in addition.

5. The authors do not discuss the significance of which pregnancy was affected by preeclampsia. Preeclampsia in the first pregnancy is more common than in later pregnancies, and preeclampsia in later pregnancies may be more difficult to separate from chronic hypertension or renal disease as well as more strongly associated with later outcomes. The proportion of women with a preeclampsia in first vs later pregnancies should be given, and the association of preeclampsia with later hypertension should be tested separately in women with preeclampsia in first vs later pregnancies.

6. The abstract should be modified to have a stronger focus on the findings for the normal definition of hypertension to give a more balanced presentation of the findings.

Minor essential revisions
1. The discussion section is very long with 6 pages. It would benefit from shortening with a stronger focus on the main findings.

Discretionary revisions
1. The authors use 34 weeks as cut-off for early-onset preeclampsia in Table 2 but very few women in this subgroup limit further analyses. I would suggest attempting 37 weeks as cut-off instead.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**
I declare that I have no competing interests