Reviewer's report

**Title:** Polymorphisms of the endothelial nitric oxide synthase (NOS3) gene in preeclampsia: a candidate-gene association study

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**Reviewer:** Kalliopi I. Pappa

**Reviewer's report:**

The manuscript by Zdoukopoulos et al. entitled 'Polymorphisms of the endothelial nitric oxide synthase (NOS3) gene in preeclampsia: a candidate-gene association study' attempts to further evaluate the association of three intergenic common NOS3 variants in preeclampsia, defined previously by the three most commonly investigated and potentially functional NOS3 variants (instead of other tested variants or HapMap tagging polymorphisms) since they aimed to actually replicate the already examined associations.

By applying conventional genetic statistical analysis, they conclude that there is no strong association of the variants with the disorder.

The research question is clearly posed by the authors and the study is well designed. The methods are well described and the data are straight forward and well documented.

However, by employing the above strategy of a single gene polymorphism (even if it includes three previously studied intergenic polymorphisms with potential functional significance), the putative significance or insights for a genetic association of the NOS3 gene with a multifactorial disease such as preelampsia are very limited. This weakness is well recognized by the authors and should be clearly phrased in the manuscript (Abstract, Results and Discussion).

The authors could consider expanding the NOS3 haplotype in the Greek population by evaluating additional SNPs flanking the NOS3 gene. The data generated by such an approach, could provide additional insights on the role and the contribution of the region on the development of preeclampsia.

Although the authors recognize the necessity of a larger sample for the increase of the power of the results, and considering the above suggestions, to my opinion the manuscript adheres to the relevant standards for reporting and data deposition and provides the impetus for expanding such studies employing multiple intergenic haplotype analysis.

Therefore, I regard the submitted manuscript acceptable for publication.

Best regards,
Kalliopi Pappa, MD, PhD

**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:**

I declare that I have no competing interests