Reviewer's report

Title: Urinary Cortisol and Depression in Early Pregnancy: Role of Adiposity and Race

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Reviewer: James Newham

Reviewer's report:

I found this a really interesting topic which the authors have clearly thought through a sound rationale for examining the association between cortisol and depression based upon a comprehensive understanding of the previous research base. However there are a number of problems with the analysis and the interpretation that need to be clarified and currently severely affect the interpretation.

Major Compulsory Revisions

The description of the timing of the cortisol measurement is severely lacking. It describes that the ‘morning spot urine sample’ was taken and maternal plasma samples were collected between 6-16 weeks gestation. First, the authors need to be explicit whether the urine and blood sample were taken at the same time. Second, and more importantly, far more detail needs to be taken regarding the exact measurement. Due to the diurnal variation in cortisol the timing of these measurements is crucial. The authors comprehensively discuss the findings in relation to cortisol awakening responses in previous cohorts but they are very unclear about when exactly these measurements were taken. A single measurement cannot be seen as indicative of the awakening response and it is the pattern of the response that is more informative than a single sample. The authors need to explain why Area-under-the-curve (AUC) analysis was not used instead of a single time point. Consequently it is difficult to make some judgements on the paper until this information is transparent.

On a similar note, the collection period of 6-16 weeks is quite significant in regards to both the development of the fetus and the mothers’ psychological state. In regards to the first point, how does this difference in time affect rates of cortisol secretion. In regards to the second point, the authors only measure depression but it should be acknowledged that cortisol may be elevated through general stress and anxiety, which may be comorbid to depression. I think this needs some attention as it cannot be presumed that just because the matched controls did not have a diagnosis of depression that they will be unstressed and so have normal cortisol levels. The authors themselves acknowledge that variations in depressive subtype may be influential but it may be more worthwhile to explain the potential influence of comorbid anxiety (http://www.ncbi.nlm.nih.gov/pubmed/18493710)

It appears there are no exclusion criteria for antidepressant medication (1
premise the line ‘collagen vascular disease (autoimmune disease) on medication’ relates only to the medication for this specific disorder). This is an important factor due to the associations between several antidepressants with weight gain. This iatrogenic cause of weight gain may interfere with cortisol secretion. Furthermore, evidence has shown that associations between depression and the cortisol awakening response may be principally due to the medication (http://www.ncbi.nlm.nih.gov/pubmed/17855000).

A major concern I have with the study is the limitations of the statistical analysis. The authors provide a power calculation to explain the number of 50 women but they do not explain the analysis this applies for. Is this to see a difference between the depressed and non-depressed? This needs to be explicit. If this is the case then it really needs to be made explicit that the study is not powered to detect differences when the groups are further divided by whether obese or not obese and this is purely exploratory. A more general point is that I find the matching of depressed to non-depressed a very crude division and may overlook the subtleties in how differences within group affect the findings. For example there is a very large outlier in figure 2. I think a hierarchal regression model would be far more robust with depression as a categorical variable entered after controlling other variables such as weight. I appreciate some of the data may be non-parametric but then bootstrapping techniques would compensate for this.

Minor Essential Revisions

Keep it simple for the reader by not removing the acronyms of PTB and LBW for Preterm birth and low birth weight. These terms are not used enough in the text to necessitate an acronym.

The figures cannot be interpreted as there is no legend describing what data points and lines represent each group. Furthermore, 3 lines exist in Figure 1 so I’m unclear what group other variable is represented.

Discretionary Revisions

Line numbers would be appreciated for future revisions to isolate where changes are needed.

The majority of the first paragraph in the Discussion is fairly obsolete. Opening with a summary of the findings would be far more useful to the reader and highlight the importance of the study.

In the discussion it states ‘we did not observe a relationship between early pregnancy cortisol (plasma or urine) and PTB or LBW’ but this finding is barely mentioned in the results. The study is very underpowered to detect such a difference between groups with these outcomes. I suggest do not make this the focus of your opening paragraph of the discussion.

There are a lot of interesting findings in this study but as a reader they sometimes get lost as it is hard to discern what is the primary outcome, secondary outcome, post hoc analysis. I suggest breaking this down more
clearly. For example, ethnicity comes across the priority, then the association between plasma and urine, then the association between adiposity and cortisol, then the influence of depression. I think if the authors are very clear about what they see as the most important finding it will make it easier to recognise the ‘take home’ message.

Despite describing the importance of examining ethnicity throughout the introduction, the fact that the sample is entirely black almost becomes obsolete. The demographics should give some clearer idea of the ethnic origin and with socio-economic status being an influential factor when examining racial disparities, this information would be useful. Even if as simple as Education levels. I think the authors can be fully justified in saying they chose to look at exclusively black women as these are an underrepresented sample at potentially higher risk but I think they need to describe it as a limitation on in the Discussion that socio-demographic factors were not fully explored.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests