Reviewer's report

Title: The HAPPY study (Holistic Approach to Pregnancy and the first Postpartum Year): design of a large prospective cohort study.

Version: 2 Date: 11 July 2014

Reviewer: James Newham

Reviewer's report:

The authors provide a protocol for a large prospective cohort study they are planning that investigates effect of maternal mood, thyroid function, human chorionic gonadotropin (HCG), and pregnancy related somatic symptoms (including nausea and vomiting (NVP) and carpal tunnel syndrome (CTS)), on pregnancy outcome of mother and fetus. I am happy to accept the protocol with minor revisions. While I appreciate that the authors have already received ethics approval for this study, I have made a number of suggestions which may entail the authors making amendments in their protocol. I do not see these as mandatory but I think these changes could strengthen potential findings at a later date and a provide a contingency if targets are not met in recruitment. I look forward to seeing the results of the findings

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1) I personally would not recommend the Generalised Anxiety Disorder Scale as this is specifically used for identifying clinical cases of anxiety disorders (which will possibly be excluded as considered high risk by criteria given in the manuscript). I would suggest a more general measure of anxiety that has been routinely studied with pregnant cohorts, such as the STAI. This is more likely to pick up greater variability in responses.

2) You may want to incorporate a measure of additional activities pregnant women engage in such as antenatal yoga and pilates. It is likely that midwives may anecdotally recommend yoga to sub-clinical stressed/anxious/depressed mothers and those with carpal tunnel syndrome.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Introduction

Due to the multi-dimensional nature of the project, a high number of concepts and mechanisms are described to the reader (e.g. mental health, physiological function, hormonal function etc). It is unlikely any reader will be entirely familiar with every aspect of this project, and also within the context of pregnancy. Therefore I think it is important that the authors are explicit on every term introduced. For myself, I am not overly familiar with thyroid function so concepts
such as hyperthyroidism could benefit from a brief explanatory sentence. In contrast psychological health is more my speciality and so some of the concepts may be obvious to me but not other readers. Nothing too in depth but a simple sentence. Many proceeding comments touch upon this main criticism

‘Maternal signs’ is an odd term that is frequently used throughout the manuscript. I’m not entirely sure what the authors are implying and this needs to be changed

Pg. 5, Line 11-12
What differentiates Hyper-emesis gravidarum from regular morning sickness? Please provide brief definition

Pg. 5, Line 20
Be more descriptive on what morphological factors may influence likelihood of CTS

Pg 5, line 23-24
Is there any previous evidence of the effects of CTS on quality of life? This is an important pathway in your model

Pg 6, line 11-15
The literature review of anxiety and depression in pregnancy is severely lacking with little description and an unawareness of the studies showing how distress is higher in pregnancy and it’s fluctuations across pregnancy (Newham and Martin, 2013). No references have been provided.

Pg7, line 17-19
This is an inefficient description of the link to infant development. This is a prime area to highlight the importance of the study as links may be due to thyroid dysfunction causing biological alterations to the child independent of maternal mood or vice versa. This should be the core of literature discussion to justify the postpartum follow up.

Pg7, Line 24
More explanation of what thyroid peroxidase enzyme (TPO-Ab) is and its implications is needed.

The section ‘Antenatal Wellbeing’ begins by describing physiological conditions of nausea and carpal tunnel syndrome which seems incongruent as wellbeing is primarily about psychological mood.

Overall I really think you should start the introduction with a brief description of the model and then describe each construct of the model so have an initial idea of how components are inter-related. So parts of Study objectives could go higher up. Unfortunately due to some of the sparse information on certain links (as described in comments above) the model doesn’t seem very cohesive so I think the argument of their inter-relations needs reinforcing early on
Methods

Give full description for acronym of HAPPY in the manuscript as only given in the title.

Will cases of pregnancy loss be excluded if later in the pregnancy? Blood samples at 10-12 weeks may be informative for identifying possible biomarkers but I think this needs explaining even if ethics meant it was not possible.

It is unclear whether it is the same blood sample that is routinely collected or an additional blood samples taken at the same time point (e.g. ‘Because all additional blood samples were obtained during regular blood assessments as part of regular obstetric care, the board confirmed that no additional approval of a medical committee was needed.’/ ‘Furthermore, at standardized blood assessment around 10-12 weeks 1 and 26-30 weeks of gestation, an additional tube of blood is withdrawn for thyroid functioning assessment and HCG analysis’). This needs to be transparent and consistent.

I think the response rate of 70% is optimistic if additional blood samples are required—even if taken at the same time points. Also it does rely on midwives actively recruiting and I think there should be some scepticism as it is not a single research midwife committed to data collection. Furthermore also the reliance of postal responses will cause a high drop out rate. To simply state ‘Based on previous pregnancy-related research experiences of the last 20 years in this area, the response rate is expected to be high (70%)’ seems a bit optimistic and referencing is required to justify this.

The authors give an admirable calculation of expected sample sizes but I think the authors should try to anticipate for lower numbers, and possible non-normality of the data, by considering bootstrapping statistical techniques which will robustly allow to make inferences when numbers do not meet expected levels and when wanting to combine parametric and non-parametric data in the regression analysis.

The term ‘all kinds of somatic symptoms’ is not very scientific and needs further clarification.

EPDS cut offs are lower than actually have been established and these need to be raised or at least rationalised in the context of research in this area (http://www.ncbi.nlm.nih.gov/pubmed/19298573). Also move the section of the EPDS in the postpartum to when discussing it in the antenatal and give appropriate cut-offs in the postpartum.

Why will the psychometric properties of the new anhedonia subscale be assessed in only a sub-sample and not the entire sample? I’m against the idea of just fusing two measures together, and assessing the psychometrics of this should be a central aspect of the project.

Pg. 20, line 20 – occurrence of stressful life events. No description of how this will be measured.
With the statistics I really think some form of pathway analysis needs to be performed, or mediation analysis to examine the inter-relations between the components of the model. I think the model in Figure 1 is central to the paper and rationale for the study. Without it, it can come across a little like a ‘data fishing’ exercise by how so many factors are examined.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

The issue of high risk cases is quite important in this protocol as it is described in Pg. 14, Line 5-9;

‘It should be noticed that in The Netherlands, 84% [24] of all pregnant women contact the primary care community midwife for a first antenatal control (usually between six to ten weeks of gestation). The other 16% who immediately contact the obstetrician at the hospital represents a relatively high risk group of women (with gemelli pregnancy or suffering from chronic diseases such as diabetes, thyroid dysfunction, psychiatric disorders) and by definition are not eligible for this study.’

First of all I am a little unclear at when a woman is defined as high risk. Does this occur at the first midwife session mentioned as I am unclear when they would be referred based on this description. International differences in practices require this is fully explained to the readers.

Secondly, and more importantly, is that by excluding these high risk cases you are getting rid of those who are most likely to show variation in thyroid function. Similarly by getting rid of those with psychiatric disorders means you are unlikely to identify those with high anhedonia scores in your sample. I think that this needs serious consideration as if no association is found it is likely to be because you are excluding the cases where this is an identified problem.

Overall though a very interesting study protocol

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests