Author's response to reviews

Title: Early nasogastric tube feeding in optimising treatment for hyperemesis gravidarum: the MOTHER randomised controlled trial (Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding)

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Author's response to reviews: see over
Dear Editor,

We are very grateful for the reviewers’ most meticulous efforts in their second review of our manuscript after our submission of a new version following the first round of review.

A point-by-point response to the new concerns raised by the reviewers is attached. We have tried to explain some methodological considerations and the language suggestions have been taken to heart. Also more details on the data collection have been provided. Unfortunately, not all suggestions could be implemented as the trial is already ongoing, but will be certainly of value for studies that will follow.

Two reviewers raised several new issues about the paper, which had not been brought up in their first review of the earlier draft. We trust that we have now addressed all the issues they raised satisfactorily.

On behalf of all co-authors,

Iris Grooten, MD
Reviewer 1: Marlena Fejzo

1. I am satisfied with the response to my review. However, I suggest that the authors have a plan to show the treatment arms are well-matched for antiemetic treatment. The authors have shown that they have a protocol in place to collect this information, but the treatments (in addition to tube feeding) for HG need to be well-matched or results adjusted if not well-matched by chance alone, in order to appropriately interpret the results.

   Reply:
   This RCT is interested in the effect of intravenous rehydration versus tube feeding on birth weight and secondary outcomes. It is unlikely that large differences at baseline in antiemetic treatment (prescribed by general practitioner previous to hospital admission) are present or otherwise would influence our outcome. We stratify for hospital of care (with possible differences in local protocol including differences in antiemetic treatment), meaning that an approximate equal number is randomized to local care and tube feeding in every centre, to minimize bias due to the multicentre nature of the trial. It is also possible that tube feeding reduces the need for antiemetic medication. Information on medication use will be collected to enable analysis and possible adjustment if medication use is considered a confounder as suggested.

2. Also, I did not see anything related to my issue #4 which was claimed to be addressed "in lines 237-238" of the manuscript. That being said, I am satisfied with page 12 of additional file 1 to address #4.

   Reply:
   Please accept our apologies for referring you to wrong line numbers. Collection of information on received treatment (including location of tube placement) is addressed in lines 202-204, in which we also refer to our CRF. Analysis of side-effects and reasons for discontinuation of the allocated treatment is also addressed in lines 236-237.

3. Finally, I highly recommend that the early nasogastric tube feeding protocol includes thiamin supplementation in all cases, as WE continues to be reported and we also have recent reports of deaths due to WE in HG patients.

   Reply:
   We agree that supplementation of thiamine is an easy and necessary measure in preventing this rare but serious complication. If the participating hospitals did not already prescribe thiamine to their patients, we have advised them to do so and refer to the risk of Wernicke Encephalopathy. However, since the trial is ongoing we are unable to make thiamine prescription obligatory for trial participation.
Point-by-point response

Reviewer 2: Siti Zawiah Z Omar

_No comments to address._
Point-by-point response

Reviewer 3: Ilan Matok

1. The authors have provided relevant, adequate and gracious responses to our queries and suggestions. The manuscript still requires a little language polishing (for example line 183 “participants will be asked informed consent” should probably be “will be asked for”). There are still some inappropriate shifts of tenses within the same context (for example, lines 140-156 shift unnecessarily between the future and present tense a number of times). Assuming the trial is already running, it might make more sense to just adopt the present tense for the description of most of the trial protocol (“study will be” in line 129 could read “is”, just like line 54, “patients will be asked” could read “are asked”, etc.). We wish the study group a safe and successful endeavour, and look forward to seeing the results of the study”.

Reply:
Thank you for your kind response and suggestions. We have altered the majority of the protocol to the present tense.
General reply:
Thank you for your thorough review with detailed suggestions. Unfortunately, some of these will be hard to address because this is an ongoing trial (first submission of the study protocol has been more than a year ago), which might have been unclear to you for which we apologise. Progression of the trial can be followed on the study website (http://www.studies-obsgyn.nl/Mother).

Many comments concern the collection of additional data. Most of this data is indeed collected. If not collected per CRF it will be per questionnaire or other form (diaries and forms to fill out by caregivers during biobank material collection). We have tried to describe most important data that will be collected in this manuscript, but the full data collection can be found in the study protocol on our study website, see http://www.studies-obsgyn.nl/upload/C1%20MOTHER%20protocol%20Version%207.1%2009102015.pdf (page 12). We currently experience that the amount of data we collect are already on the limits of what participants can handle (especially when feeling ill) and are realistic in terms of logistics and finances. Experiences from this trial will certainly teach us what is the best way to collect information and what information should be further enquired to address specific questions.

1. Regarding the validation of the PUQE-24 scale, please ensure it encompasses the full scoring system. A recently published Norwegian PUQE validation study by Birkeland et al, excluded the question pertaining to sleep (How many hours have you slept out of 24 hours? Why?) which is part of the PUQE-24 scale. The question on sleep is very important as women may or may not be sleeping well, they may be experiencing nausea and/or vomiting at night which may be more related to heartburn and reflux symptoms, insomnia, children waking them up, etc… which would increase their symptoms of nausea the following day. Additionally, the authors also changed the Wellbeing question to quality of life. Please see page 804 from paper to ensure proper translation of the scale: Ebrahimi N et al. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. J Obstet Gynaecol Can. 2009 Sep;31(9):803-7.

Reply:
Unfortunately, like Birkeland et al, we have not included the question on sleep, nor on wellbeing due to overlap with other questionnaires. We decided to use the PUQE-24 score to quantify nausea and vomiting. Both NVPQoL and HIS are used to investigate the impact on daily functioning and wellbeing, items that are also (partly) addressed in the HADS and SCL-90. Furthermore, the EQ5D uses a scale (0-100) to measure wellbeing.

2. I disagree with the authors’ response to my question pertaining that women should be excluded when their NVP symptoms begin for the first time after 10wks of gestation. Up to 85% of women, will experience varying degrees of severity of nausea and vomiting of pregnancy (NVP) before their 9th week of gestation, which may or may not progress to the most severe form hyperemesis gravidarum (HG) which requires hospitalization (up to 2% of women). NO woman starts initially with HG. There are many clinical practice guidelines and many published papers discussing differential diagnosis, stating that if NVP symptoms begin for the first time after 9-10wks of gestation symptoms are due to other causes. Women could be hospitalized before their 20th week of gestation however, it is important to assess all participants in the study for their NVP start date.

Reply:
Unfortunately, an international definition for HG is currently lacking to guide us in patient eligibility. We have pragmatically chosen to define ‘HG’ as it has frequently been defined in the literature: it is a clinical diagnosis for hospitalisation for vomiting in pregnancy after exclusion of other causes of nausea and vomiting in pregnancy (which are formal exclusion criteria), despite not explicitly questioning and excluding patients when symptoms occur for the first time after 10 weeks gestation.
We are however collecting data on the timepoint at which they experienced nausea and vomiting symptoms for the first time in pregnancy, so we will be able to investigate the issue of HG definition retrospectively.

3. Regarding the Case Report Forms, I believe they should be more detailed information taken.
   a. A medical history detail seems very limited. They should also include insomnia, migraine, IBS, celiac, heartburn, indigestion, anemia, hypoglycemia, motion sickness, h.pylori infection, etc. For example, when women become pregnant, they may develop symptoms of heartburn/reflux, insomnia or motion sickness. Those are all important to note and will greatly impact their symptoms. New meta-analysis published on helicobacter pylori and HG: Li et al. Helicobacter pylori Infection Is Associated with an Increased Risk of Hyperemesis Gravidarum: A Meta-Analysis Free PMC article: http://www.hindawi.com/journals/grp/2015/278905/
   b. Also, there should be a question on “any viral or bacterial infection(s)?”
   c. There should be a question pre-pregnancy weight and current weight in order to assess BMI.
   d. There should also be questions on weight, fluid intake, urine output, hours of sleep, and sleep patterns at initial and at each call or follow-up.
   e. There should be a question on street drug use, such as marijuana, opioids, ghb, cocaine, etc.
   f. There should be a question on other vitamins or supplements taken
   g. There should be a question on what non-medical approaches they have tried or currently on.
   h. Regarding to the antiemetic question, are phenothiazone prescribed to women?
   i. Are there any other antiemetics?
   j. In North America, there are serious warnings and caution for metoclopramide (Primperan) such as, boxed warning for tardive dyskinesia by the FDA and metoclopramide induced depression has occurred in patients with or without a prior history of depression. Are there the same cautions and warnings in the Netherlands? This may impact the study, as the treatment may induce depression even prior to admission, or may occur if given in hospital.
   k. Regarding the APGAR score, why are the authors only using 5 min? A recently published paper by Rudiger et al "Neonatal assessment in the delivery room – Trial to Evaluate a Specified Type of Apgar (TEST-Apgar)" [NCT00623038] demonstrated that a combined APGAR is a better tool. Free PMC: http://www.biomedcentral.com/1471-2431/15/18
   l. There should be a question on length of baby
   m. There should be a question on head circumference
   n. In maternal background, in the relationship section, there should also be a question on “married”
   o. There should be a question on what kind of work the women do, if working
   p. There should be a question if they have taken any time off or sick leave due to their symptoms

Reply:

Thank you for your detailed comments. Most of the information suggested above is indeed collected (a, b, c, d, f, l, m, n). It is indeed a good suggestion to have information on drug use (especially cannabis) (e), we therefore have added a question to the CRF (page 6). Regarding antiemetics, phenothiazone (h) are not commonly prescribed for HG treatment, but metoclopramide (j) is often used as first choice (outpatient and in hospital). The HADS questionnaire is enquired several times to inform us on depressive symptoms over time (0, 1 and 3 weeks after inclusion, post-partum and 1 year post-partum). It is a good suggestion to be aware of the possible interaction between metoclopramide and depressive symptoms. The ability to work is shortly addressed in the HIS and SF-36, but we do not collect detailed information on work and time lost from work to enable a proper cost effectiveness analysis. This would be something for future studies, as is a detailed data collection on sleep behaviour of HG patients. The publication on Apgar score referred to has occurred after the trial has commenced but is certainly of value for future studies.

Discretionary Revisions
1. Regarding the psychopathology scales, it may be useful to incorporate the Edinburgh Postnatal Depression Scale (EPDS) at initial enrolment and each follow-up time point. This scale is validated for pregnancy and post-pregnancy, please see link https://psychology-tools.com/epds/. Additionally, please have a look at paper by Bozzo P et al, Nausea and vomiting of pregnancy (NVP) and depression: cause or effect? Clin Invest Med. 2011 Aug 1;34(4):E245. Please also have a look at study by Aksoy et al: Depression levels in patients with hyperemesis gravidarum: a prospective case-control study. Free PMC article http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308584/

2. A recently published study which may be of interest to the authors and to possibly consider adding ALT to routine laboratory. Chraïbi Z et al. Hyperemesis gravidarum: a ten-year French retrospective study of 109 patients state the following conclusion: “…. hyperemesis gravidarum in our center is frequently associated with a non-French origin, and that abnormal liver function tests and decreases of prothrombin time are common in this condition. Our results suggest that increased ALT is a factor of severity in hyperemesis gravidarum.” http://www.ncbi.nlm.nih.gov/pubmed/25511653

3. Regarding follow-up of infants, authors mentioned that funding has not been obtained. I would like to suggest that if investigating neurodevelopment of children, to not only look at HGs impacts in pregnancy and offspring, but it would be very interesting to assess both maternal and paternal IQ and their education. For example, a study by Meador et al, state “both maternal IQ and education are independently related to child cognitive outcome and both should be assessed in studies investigating the effects of fetal drug exposures or other environmental factors that could affect the child's cognitive outcome”. There are numerous studies investigating parental age (paternal and maternal) and neurodevelopmental disorders, and a recent study by D’Onofrio et al demonstrated that paternal age is associated with increased psychiatric and academic morbidity in offspring.

Reply discretionary revisions:
Thank you for your suggestions for further reading. The EPDS would be a useful suggestion for a future study, perhaps on psychological interventions for HG. ALT (ALAT) is collected per CRF. Neurodevelopmental assessments of infants would indeed – although costly – be very interesting. We might contact you in the future for collaborative HG research.