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)

Authors:

Iris J Grooten (i.j.grooten@amc.uva.nl)
Ben Willem J Mol (b.w.mol@amc.uva.nl)
Joris AM van der Post (j.a.vanderpost@amc.uva.nl)
Carrie Ris-Stalpers (c.ris@amc.uva.nl)
Marjolein Kok (m.kok@amc.uva.nl)
Joke MJ Bais (j.m.j.bais@mca.nl)
Caroline J Bax (c.bax@vumc.nl)
Johannes J Duvekot (j.j.duvekot@erasmusmc.nl)
Henk A Bremer (h.bremer@rdgg.nl)
Martina M Porath (m.porath@mmc.nl)
Wieteke M Heidema (wieteke.heidema@radboudumc.nl)
Kitty WM Bloemenkamp (k.w.m.bloemenkamp@lumc.nl)
Hubertina CJ Scheepers (h.cj.scheepers@mumc.nl)
Maureen TM Franssen (m.t.m.franssen@umcg.nl)
Martijn A Oudijk (m.a.oudijk-3@umcutrecht.nl)
Tessa J Roseboom (t.j.roseboom@amc.uva.nl)
Rebecca C Painter (r.c.painter@amc.uva.nl)

Version: 6
Date: 24 August 2015

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

We are very grateful for the thorough review by all reviewers of our study protocol we have received.

Attached you will find a point-by-point response to the concerns raised by the reviewers. Many questions were asked about the detail of data collection. To our opinion, describing the data collection in such detail would not contribute to a clear publication. Instead, we have added a brief summary of collected data in lines 198-204 and supplemented our Case Report Form (additional file 1), in which exactly can be seen to which detail data will be collected. Furthermore, the full protocol can be downloaded from our study website, see lines 280-281. For clarity, we have inserted table 1 in the main body of the article.

Hoping to have addressed all questions sufficiently,

On behalf of all co-authors,

Iris Grooten, MD
Reviewer 1: Marlena Fejzo

1. The main issue with the study design is an existing problem: "standard of care," for HG includes many different treatments and medication options which may lead to great variability in the study arms. The only ways around this issue that I can think of are to 1) use either no antiemetic treatment or 2) use no antiemetic treatment for the first week and then document any future need for antiemetic as an outcome measure, or 3) use a single treatment protocol/antiemetic in both arms, or if this is not possible, 4) to at least have very well defined record keeping that compares each treatment/antiemetic used, dosage, and duration AND to make sure to note any need for change or additional medications needed during the study period. The need for additional treatment/medication can and should be a secondary outcome measure of the study to show one arm works better than another. There needs to be a protocol to make sure accurate record keeping is kept even if new antiemetic prescriptions are given outside of the hospital setting to treat HG. I suggest you make a checklist of intravenous hydration, electrolyte supplement, vitamin supplement, medications, and treatments that may be given to the participant that they can fill out with their provider that includes daily dosage and duration/changes in treatment. The study may not be valid if the arms do not end up significantly well matched for which “standard of care” (ie initial treatment/medication), so you may want to re-investigate your sample size with that potential problem in mind.

Reply:
For practical reasons we have opted for option 4. Although antiemetic treatment will be given according to local care, we will collect detailed information on medication use, intravenous rehydration and tube feeding regimen and duration, vitamin supplements etcetera through our Case Report Form (CRF; see additional file 1). Furthermore, antiemetic medication use is weekly enquired via the participants diary. Details on tube feeding will additionally be recorded by the dietician and supplemented to the CRF. See added information in lines 192 and 198-204.

2. The other issue is the inclusion of multiples. I would exclude multiples from participation in the study since maternal and fetal complications, weight gain and other outcomes between singleton and multiple births are not comparable. If by chance you end up with several multiples in one arm and few or none in the other, it can seriously skew the results.

Reply:
We fully understand your concern. However, we intended to design the trial for all hyperemesis (HG) patients, thus also for women pregnant of multiples who might more frequently suffer from HG and are too in need of evidence based treatment options. Because indeed multiple pregnancy affects birth weight, we will evaluate twin pregnancies in both treatment arms and might exclude them from birth outcome analysis.

3. You may want to exclude patients with diabetes since it may be linked to an increased risk of complications such as infections from enteral feeding.

Reply:
The NICE guideline on nutrition does not state diabetes is a contraindication for enteral tube feeding, we therefore have decided not to exclude these women from the trial (National Institute for Health and Clinical Excellence: Nutrition Support in Adults: NICE Guideline CG32. London (UK): NICE Clinical Guidelines; 2006). However, side-effects of tube feeding will be evaluated.

4. Please consider making sure to include statistics on intolerance to nasogastric tube and need for change to nasoduodenal or nasojejunal insertion as this information can also be a very informative outcome of the study.

Reply:
Indeed this is very important information which we will analyse, see lines 237-238 (in more detail described in our CRF, additional file 1, page 12).
Reviewer 2: Siti Zawiah Z Omar

In contemporary studies, nausea and vomiting of pregnancy (NVP) affects 78–89% of pregnant women [1,2]. NVP starts in the first trimester in 99% of the affected women. Although there are regional and ethnic variations, hyperemesis gravidarum is generally accepted to affect 0.3–2% of pregnancies. Generally, the symptoms of nausea and vomiting decrease as the pregnancy advances. In NVP, the condition resolves in 60% of affected pregnancies by 12 weeks gestation and in over 90% by 16 weeks, whereas in contrast, for hyperemesis gravidarum cases typically only 25% resolve by 12 weeks and in 50%, symptoms may persist beyond 16 weeks.

1. Hence it would be more discretionary to state the exact criterion for the recruitment of HG cases vs NVP.
   Reply:
   For this reason, we only include women with nausea and vomiting symptoms in need of hospital admission (without other reasons for admission). Women with mild symptoms (e.g. NVP) would thus not be included. Furthermore, there is no gold standard to discriminate between NVP and HG. Would this be based on duration of symptoms, the diagnosis could only be made retrospectively, which makes it difficult to use for in- or exclusion in the trial.

2. Starting from 5 weeks gestation might be too early and would lead to more recruitment but attrition rate would be higher as most viable pregnancies (intrauterine) are diagnosed at 6 weeks gestation.
   Reply:

3. Including multiple pregnancies and getting same objective / endpoints may Not be a good idea as we definitely know multiple pregnancies result in different hormonal changes and outcome (smaller fetuses, lower birthweight, premature labours etc).
   Reply:
   We fully understand your concern. For motivation see reply at question 2, reviewer 1 (page 2).

4. Reference No: 10 year of publication not listed. Also please ensure all publication years are in correct order.
   Reply:
   Changes are made accordingly.
Reviewer 3: Ilan Matok

1. The protocol assures us that nasogastric feeding is safe. We believe that known potential adverse effects of nasogastric feeding (such as tracheopulmonary complications, enteral complication etc.), however rare, should be noted at least briefly, and recognized as a possible risk.
   
   Reply:
   We have added a sentence on complications, see lines 157-158.

2. The trial outcomes of interest include “costs” however we did not notice any definition of this outcome (Cost for the patient? For the hospital? For the Insurer? Direct/indirect costs?), or any description of the method by which this will be evaluated.
   
   Reply:
   Thank you for this good question. We originally envisioned to evaluate direct and indirect costs, however, we do not enquire for example sick leave (which would require another questionnaire). This complicates the evaluation of indirect costs. Not being able to perform a proper cost analysis, we will exclude this analysis from the current protocol.

3. Though the randomization procedure is likely to eliminate selection bias, we believe that, if possible, it would be prudent to record patient characteristics known to be associated with HG, and presumably HG severity (such as multiple gestation, gestational week, BMI etc.), and with low birth weight. Equality in group allocation with regard to important factors could then be demonstrated, and if necessary significant differences between groups could be controlled for. If the trial plan already includes the collection of this data, we believe it would be best to stipulate and address this explicitly (i.e. by adding a paragraph detailing known/suspected predictors of HG and of neonatal birth weight and the method by which they will be collected).
   
   Reply:
   We have added a section in the data collection paragraph as suggested, see lines 198-204.

4. In addition, the un-blinded nature of the trial design and the open nature of the treatment protocol, can easily lead to significant differences in “standard care” between treatment arms. This concern might be partially alleviated via the stratification procedure, which can help reduce bias arising from differences between treatment centers. However we believe it would be prudent to record treatments that may have an impact on the outcomes in question (such as use of anti-emetic medication or vitamin supplementation), and that were utilized during the study. If the plan already includes the collection of this data, we believe it would be best to stipulate and address this explicitly.
   
   Reply:
   See also lines 198-204.

5. Lastly it should be noted the manuscript requires some additional editorial “polishing” (there are inappropriate use of tenses, for example in lines 141-143; lines 172-175 are incomprehensible; line 237 “urge” should probably be changed)
   
   Reply:
   As suggested we have edited these sentences.
1. **For the primary outcomes, the authors state that the validated PUQE score will be used. However, the authors are not using the correct version of the PUQE scale. The authors need to change to the PUQE-24 scale. Please look at the following paper and Table 1 in the paper: 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:**
   We apologise for being unclear. Indeed we are using the PUQE-24. We have inserted the suggested reference and changed ‘PUQE into PUQE-24’ in the protocol.

2. **Authors have neglected to include the following study: Vander Pleog N, Gulley JM. Treatment of hyperemesis gravidarum with nasogastric feeding. Nutr Clin Pract. 1993 Feb;8(1):33-5**

   **Reply:**
   We have included the suggested reference. We have also included a new publication (Stokke G, Gjelsvik BL, Flaatten KT, Birkeland E, Flaatten H, Trovik J: Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10-year retrospective cohort study. Acta Obstet Gynecol Scand 2015, 94:359–367).

3. **Will all maternal demographics be collected, such as education, marital status, work, gravidity, parity, BMI, vitamin use pre-pregnancy, smoking, medical history, etc…?**

   **Reply:**
   We will indeed collect this information from medical records (see our CRF, additional file 1). Details on education, marital status and work will be collected via the questionnaire at randomisation. See lines 198-204.

4. **Many women stop taking their medications when they become pregnant, due to fear that it may affect the baby. How will that be assessed? Will women be treated or asked to resume their medication(s)? For women with pre-existing history of depression and/or anxiety, how will they be counseled and/or treated?**

   **Reply:**
   The trial does not interfere with prescription of antiemetics or interventions for depressive symptoms (all according to local care). However, we will enquire whether antiemetics have been used prior to admission (see additional file 1), and whether participants have (a history of) psychiatric disorders, because we are certainly interested the relationship between psychiatric disorders and HG. For this reason we use psychometric questionnaires on several occasions. To our opinion it is inappropriate to test multiple interventions in one trial. Thus evaluating psychosocial counselling and/or drug therapy would be something for a next trial (when analysis of psychometric questionnaires of this trial would suggest such a need).

5. **If the women score high in the psychopathology scales, will they be provided psychological counseling and/or antidepressant/anti-anxiety medication(s)? Experiencing hyperemesis gravidarum (HG) may cause women to be more depressed, however, if they have an existing history of depression, their symptoms could spiral to greater depression, hence increasing their NVP/HG symptoms.**

   **Reply:**
   See answer question 4. As explained, psychometric questionnaires are used for data collection and analysed at the end of the trial.
6. The authors' exclusion criteria for study should also include if NVP symptoms begin for the first time after 10 weeks of gestation. How will differential diagnosis for NVP/HG be assessed for the participants?

Reply: Based on available literature, we believe a diagnosis of HG can be made if symptoms of nausea and vomiting necessitate hospital admission (and thus discriminates between NVP and HG) for the first time before 20 weeks gestation (Fairweather criteria). Unfortunately, no gold standard for HG diagnosis is available, leading to different opinions on whom to in- or exclude. See also reply reviewer 2, question 1.

7. It is concerning when a woman is hospitalized or readmitted at 5+0 weeks (as per the inclusion criteria), as typically, nausea and vomiting of pregnancy (NVP) begins between 4 and 9 weeks of gestation and symptoms (nausea, vomiting and/or retching) peak between 7 and 12 weeks of gestation. How can this be explained? What is the inclusion criterion for start of NVP symptoms?

Reply: Although uncommon, hospital admission for HG has been described in literature from 5 weeks gestation onwards (see reply reviewer 2, question 2), this is why we will include women admitted to hospital for HG between 5-20 weeks gestation. There is no ‘minimum duration’ of NVP symptoms to be included in the trial, just the need for admission based on the patients’ condition (such as dehydration or electrolyte disturbances), at the decision of the attending physician.

8. Are women undergoing fertility treatment included? If yes, then please state fully all criteria for participation in the study. Additionally, fertility drugs increase symptoms of NVP. Authors should ensure to report women who had fertility treatment(s).

Reply: Women pregnant after fertility treatment are also eligible for participation, thus fertility treatment is no exclusion criterion. Mode of conception is indeed enquired.

9. How will dietary intake be assessed for the woman prior to their hospitalization? Will women be asked how often they were eating and drinking fluids throughout the day when they found out they were pregnant?

Reply: Participants will fill-out their dietary intake on a weekly basis from randomisation onwards. A question on whether their dietary intake is less, equals or is more than their usual intake prior to pregnancy is included.


Reply: The publication by niemeijer et al was conducted by our research group. Indeed we are very interested in the presence of Helicobacter pylori in HG patients. We plan to evaluate H. pylori serology in maternal biobank samples collected in this trial. Investigating treatment of H. pylori infection in HG patients in a subsequent trial is high on our priority list.
11. If a woman is tested positive for Helicobacter pylori infection, will she receive antibiotics?

Reply:
Only when the attending physician would want to do so. This is not common practice in the Netherlands in pregnant women.

12. Many pregnant women do not recognize symptoms of heartburn, dyspepsia or reflux (such as burping, nausea at night, belching, something stuck at back of throat, etc...), which affect 40-85% in the first trimester. In 2009, Gill and colleagues demonstrated a reduction of the NVP severity when adding acid-reducing pharmacotherapy to the existing antiemetic regimen(s). It may be beneficial for authors to ask the participants if they are experiencing any symptoms, and if yes to treat with an H2 Blocker and/or PPI.

Reply:
Medication will be prescribed according to local practice. We enquire what medication has been prescribed.

13. Additionally, with all the excessive vomiting, a woman’s throat becomes raw. She will be afraid to eat or drink. It may be beneficial for the participants to receive an H2 Blocker and/or PPI in their IV and to continue their use once sent home.

Reply:
See reply question 12.

14. The authors state “Standard care consists of intravenous rehydration and, when considered necessary, laboratory monitoring, electrolyte and/or vitamin supplementation, antiemetic medication and dietetic advice”, however, there is no information on the antiemetics that will be given, dietary advice, oral electrolytes provided, vitamins, etc... that will be provided? What are the guidelines/protocol? Please see paper by Lamondy, Anne “Hyperemesis Gravidarum and the Role of the Infusion Nurse”

Reply:
For pragmatic reasons we have decided that participating hospitals may treat their HG patients according to their own protocol in terms of iv rehydration solution, type of antiemetic’s prescribed, type of tube feeding formula etcetera. This may thus vary between hospitals. We enquire all local protocols and individual treatments given (see our CRF, additional file 1).

15. Will any of the women receive ondansetron? If yes, how will these patients be monitored? Will there be an ECG be done prior to its use? With its conflicting safety profile, and recent papers demonstrating increase risk of cardiac defects, how will participants be informed about safety?

Reply:
If Ondansetron would be prescribed, this would be according to local protocol. ECG evaluation would then be performed at the decision of the attending physician.

16. Will the participants, once sent home, continue with dietary changes, oral electrolyte solutions, antiemetics?

Reply:
Normally yes, according to the local protocol some antiemetic’s might be stopped at discharge while others might be continued. We evaluate intake and antiemetic’s used weekly until 20 weeks gestation.

17. The authors should clarify what the following acronyms/abbreviations HIS, NVPQoL, HADS, SCL-90, SF-36, EQ5D, are in the data collection paragraph in methods/designs.

Reply:
Changes are made accordingly.

18. Authors stated that the patients will be provided information in Dutch and English. Will any of the questionnaire the authors have listed for this study [validated NVP symptom and NVP specific quality of life measures (PUQE, HIS, NVPQoL), psychopathology (HADS, SCL-90) and general health related questions (SF-36, EQ5D)] be provided only in English? Have any been translated to Dutch? If yes, has it been validated?
Reply: We are currently validating the PUQE-24, HIS and NVPQoL. The other questionnaires are commonly used and have been validated in Dutch.

19. Please revise the reference #15, as the correct listing of authors are “Hsu JJ, Clark-Glena R, Nelson DK, Kim CH.”
Reply: Thank you for your detailed review. The order of authors has been corrected.

20. If long-term follow-up will be done, such as neurodevelopment of child, will the authors also test for maternal IQ and socioeconomic status?
Reply: Maternal IQ is not tested at the moment. If we plan to evaluate neurodevelopment of the child at follow up, we could then measure maternal IQ. Socioeconomic status is measured by education level and postal code.