Reviewer's report

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)

Version: 5 Date: 17 April 2015

Reviewer: Caroline Maltepe

Reviewer's report:

Major Compulsory Revisions

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.

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.

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.

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 phenothiazines 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

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

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.

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

**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'