Editorial

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The dilemma of hyperemesis gravidarum: more answers, and more questions

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Nausea and vomiting affect ≤80% of pregnancies, with the severe form, hyperemesis gravidarum, affecting 0.3–3%. The definition of hyperemesis gravidarum varies but generally involves persistent vomiting, a clinical measure of starvation (electrolyte imbalance or ketonuria), and weight loss, usually ≥5% of prepregnancy weight (1–3). Hyperemesis continues to be a challenge to manage. It is one of the most common reasons for hospital admission in the first trimester (1). Its consequences can be severe for maternal physical health, mental health, and socioeconomic functioning, as well as for neonatal outcomes. Hyperemesis is associated with anemia, rare complications from vitamin deficiency, severe depression, social dysfunction, anxiety and depression, and fetal complications related to preterm delivery and low birth weight (2, 3). Unfortunately, multiple systematic reviews in this area have concluded that, overall, there is low-quality evidence to support any one intervention to improve this condition (1, 4). There are a limited number of placebo-controlled trials and inconsistencies in inclusion criteria for trials as well as in outcome measures. In addition, although the majority of studies have reported on antiemetic therapies in different combinations and comparisons, there have been limited studies on auxiliary interventions such as intravenous fluids, outpatient management strategies, and other adjunctive measures (1, 4).

The study in this issue of the Journal by Grooten et al. (5) is notable in exploring a thus-far poorly studied intervention, enteral feeding, to improve hyperemesis gravidarum. Typically, enteral feeding is reserved for severe cases who are unresponsive to initial therapies of intravenous hydration and antiemetics, with continued severe symptoms, weight loss, and inability to tolerate oral intake (2, 3, 6). Even in that setting, the quality of evidence is low, with previous studies generally involving small, uncontrolled retrospective cohorts and no previous randomized trials (7–11). In all of these previous studies, women who received enteral nutrition failed more conservative management with intravenous fluids, antiemetics, or both, and had a more severe initial presentation of symptoms than those managed with intravenous fluids. One of the largest cohort studies thus far compared enteral nutrition, intravenous fluids, and parenteral nutrition in a retrospective uncontrolled fashion and found that, although women with enteral nutrition had a more severe initial presentation than those receiving intravenous fluids, they were ultimately able to achieve similar maternal and neonatal outcomes (12).

Grooten et al. examined whether early enteral feeding in addition to standard care compared with standard care alone would improve infant birth weight for women hospitalized for hyperemesis gravidarum. The outcome of the study at hand has a number of notable findings. There was no difference in the primary outcome of birth weight or in secondary outcomes relating to hospital readmission rates, severity of nausea and vomiting symptoms, or quality-of-life measures. Enteral feeding was associated with a significantly higher rate of side effects, although not with an increase in serious adverse events. These findings should be taken in the context of the trial: women with more severe symptoms chose to participate initially, and approximately one-third of the women allocated to enteral feeding discontinued therapy early due to side effects. A sensitivity analysis showed that women with more marked weight loss were more likely to tolerate enteral feeding (5).

There are a number of limitations of this trial. Previous systematic reviews have been limited by heterogeneity in the inclusion criteria, and this study suffers the same limitation. Hyperemesis gravidarum was not defined by any objective measure, which limits the external validity of the trial. In addition, the selection of the primary outcome is notable. Although birth weight is a useful objective measure, the most common impact of hyperemesis gravidarum is the severity of symptoms and psychosocial effects. Most previous trials on hyperemesis used some measure of nausea or vomiting severity as the primary outcome (1). Unfortunately, there was a low response rate in their assessment of these measures, so although they were prospectively powered to detect a difference in PUQE (Pregnancy-Unique Quantification of Emesis and nausea) score, the poor response rate led this study to be underpowered in that important area. Finally, as described above, the poor protocol adherence limits the interpretation of the results; however, it highlights the difficulty of universal enteral feeding, which, in and of itself, is an important clinical finding.

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Despite these limitations, this study is an important contribution to the field for a number of reasons. First, the lack of benefit found for enteral feeding in this unique randomized controlled trial supports current protocols for intravenous hydration and antiemetic therapy before enteral feeding (2, 3, 6). Second, as a randomized trial, it highlights the potential selection and reporting bias of previous retrospective studies. The patient selection in previous retrospective studies was distinct in that they included women who had otherwise failed initial standard therapy and thus cannot be compared directly with this trial. This applies to both the findings of benefit as well as patient tolerance of the intervention. Third, the sensitivity analysis suggests that those with marked weight loss may be a subgroup who will benefit from early enteral feeding and highlights an area of further study. Fourth, although consistency in the inclusion criteria and primary outcomes for trials on hyperemesis continues to be a challenge, the assessment here of a range of maternal and perinatal outcomes most likely to be affected by hyperemesis is notable and should be replicated in future trials.

Grooten et al. have provided thus far unavailable level I evidence to support previously recommended protocols of expert opinion (2, 6) that enteral nutrition may be reserved for those who fail intravenous hydration, antiemetic therapy, or both; and given the rate of side effects and patient tolerability, it should not be a first-line therapy. The lack of a significant increase in serious adverse events compared with standard care in this randomized trial supports the continued use of enteral nutrition as a safe option when necessary. Their results open the door for further randomized studies on enteral nutrition. Future areas of research should address the question of when to initiate enteral feeding—after 48 h, after 1 wk? Further elucidation of this area would provide important clinical benefit in clarifying the management of hyperemesis. In addition, further study in the subgroup of women with documented severe features (i.e., documented weight loss) is suggested by the sensitivity analysis. Finally, given that enteral nutrition does not appear to be beneficial as a first-line therapy, further well-designed randomized controlled trials should be encouraged on other first-line therapies, such as exploring various options for rehydration, nutritional support, and symptom control in the severe condition of hyperemesis gravidarum.

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