Barriers and challenges in hyperemesis gravidarum research
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Summary, general discussion and future implications
SUMMARY

In chapter 1, we identified several problems that may hamper progress in hyperemesis gravidarum (HG) research and patient care. We address these problems in the research projects included in this thesis and a summary of our findings is given below:

Part I studies the potential of biomarkers for HG diagnosis and prediction of disease severity. In chapter 2 we systematically reviewed the available evidence of aetiological, diagnostic, prognostic and predictive studies of biomarkers for either the presence or severity of HG or nausea and vomiting in pregnancy (NVP). We identified 81 articles on 9 biomarkers, including chorionic gonadotrophin, thyroid hormones, leptin, oestradiol, progesterone, white blood count, lymphocytes, ketonuria and Helicobacter pylori (H pylori). Of the reviewed biomarkers, only H Pylori showed a clear aetiological association with HG but a sensitivity of 73% and specificity of 55% limits its diagnostic value. Despite its widespread use, we found no evidence for the use of ketonuria, nor for other biomarkers, to diagnose or predict severity of HG. In chapter 3 we further explored the association of H pylori infection with vomiting severity on pregnancy and birth outcomes in a large population-based prospective cohort of pregnant women (n=5549). The results of this study confirm that H pylori is an independent risk factor for vomiting in pregnancy. Furthermore, we found that in women with daily vomiting, H pylori is also associated with low maternal weight gain, reduced birth weight, and small for gestational age.

Part II investigates treatment options for HG. In chapter 4 we systematically reviewed the effectiveness of corticosteroids (CCS) for HG. The use of CCS for HG has been advocated because CCS are effective in reducing chemotherapy-induced nausea and vomiting. We identified five trials examining the effects of CCS in women with HG (n=310). Meta-analysis was possible for one outcome and showed no significant effect of CCS on hospital readmission rates. Two small studies reported a reduction of vomiting episodes and one found improvement of wellbeing, but no effect on other outcomes. None of the studies that investigated perinatal outcome found an effect of CCS and were underpowered to investigate teratogenic effects. Studies were of low quality and likely subject to publication bias. Based on these findings, there is currently insufficient evidence to support CCS treatment for HG. In chapters 5 and 6 we present the study protocol and results of a randomised controlled trial (MOTHER) respectively, in which we assessed the effectiveness of early enteral tube feeding in addition to standard care with intravenous rehydration and antiemetic treatment, or standard care alone, for maternal and offspring outcomes. Although adequate intake of energy and nutrients during pregnancy is vital for adequate maternal weight gain and foetal growth, no previous randomised controlled trials (RCT) have studied a nutritional intervention...
for HG. We performed a multicentre open-label RCT in 19 hospitals in the Netherlands. Women hospitalised for HG between 5 and 20 weeks gestation (n=116) were randomly allocated to enteral tube feeding for at least 7 days in addition to standard care with intravenous rehydration and antiemetic treatment, or standard care alone. The primary outcome, birth weight, was similar for both treatment groups. Secondary outcomes including maternal weight gain, duration of hospital stay, readmission rate, nausea and vomiting symptoms, quality of life, psychological distress, prematurity and small for gestational age were also comparable. Unexpectedly, many women discontinued tube feeding due to discomfort. We therefore concluded that in women with HG, early enteral tube feeding does not improve birth weight or secondary outcomes and is poorly tolerated as standard treatment for HG.

Part III explores whether symptoms related to HG and hospital admission for HG are associated with long-term adverse cardiometabolic health in offspring, as previous evidence suggests that malnutrition in early pregnancy increases the risk of cardiovascular disease in offspring later in life. In chapter 7 we studied the association of early pregnancy weight loss with birth outcomes and markers of cardiometabolic health in a Dutch prospective cohort of pregnant women and their children (n=7818), followed until the age of 5-6 years (n=3165). Birth outcomes were not different for children born to mothers with and without early pregnancy weight loss. At follow-up, cardiometabolic markers including body mass index (BMI), glucose and lipid levels were neither different, but blood pressure was increased in children born to mothers with early pregnancy weight loss. This suggests that early pregnancy weight loss, often occurring as a manifestation of HG, could have long-term consequences for offspring cardiometabolic health. In chapter 8 we assessed whether similar findings may be present in adolescents, born to mothers who were hospitalised during pregnancy for HG. We used data of mothers (n=8953) and adolescents at 16 years of age (n=6462), who participated in a Finnish birth cohort. Unlike the findings in chapter 7, none of the cardiometabolic markers were different for adolescents born to mothers with and without hospitalisation for HG. Consequently, we are unable to confirm that prenatal exposure to HG affects cardiometabolic health of offspring at the age of 16 years.

Part IV considers the lack of consensus on HG definition and trial outcomes and proposes suggestions how to improve HG research and patient care. In chapter 9 we systematically described the variation in HG definition and outcome reporting in RCT’s studying any intervention for HG. We identified 37 trials. None of these trials used an identical set of items to define HG. In total, 11 definition items (54 item measures) and 33 outcomes (75 outcome measures) were reported. The substantial variation in HG definition results in heterogeneous study populations, which limits the generalizability of trial results, while variation in outcomes reported affects the ability
to perform evidence synthesis in meta-analysis. In chapter 10, the current chapter, we first summarised the results of all research projects included in this thesis. In the next section we will continue to discuss our findings and future implications for HG research and patient care.

GENERAL DISCUSSION AND FUTURE IMPLICATIONS

Today, the principles of evidence based medicine (EBM), introduced in the 1990’s by Guyatt and colleagues, have been widely recognised as the cornerstone of medical practice. EBM not only advocates the integration of individual clinical expertise and the best available evidence, but also stresses the importance of practice guidelines to enhance quality of care and shared decision-making through recognition of patient values and preferences. Unfortunately, the principles of EBM seem to have bypassed the understanding and management of HG on all levels.

Implications of lack of evidence for diagnosis and treatment

Understanding of the aetiology of HG is limited to the fact that this is likely multifactorial. Not knowing the causes of HG clearly impacts diagnostic work-up. No diagnostic test is available to confirm the presence of HG and evaluation of the literature has not proven otherwise. In current clinical practice, ketonuria is often used to diagnose HG or to time hospital discharge, but these clinical decisions are not supported by evidence. The absence of a diagnostic test implies that diagnosis relies on clinical characteristics. In contrast to other medical conditions defined by clinical criteria, such as rheumatoid arthritis and acute respiratory distress syndrome, very little has been done to develop standardised diagnostic criteria. This results in a wide variety of items that might qualify a woman as having HG, which leads to clinical diagnostic variation, as well as study incomparability.

Treatment of HG is empirical and therefore likely suboptimal. The lack of curative treatment options and resistance to pharmacologic interventions in early pregnancy among caregivers and patients may lead to ‘therapeutic nihilism’. Difficulties implementing EBM may arise when high quality evidence is lacking. Treatment of HG with CCS for example, has been advocated by Jarvis and Nelson-Piercy based on their own findings of a small trial (n=24) in which CCS improved maternal well-being, food intake and weight gain. Yet attempts to confirm the effectiveness of CCS in later systematic reviews failed due to low study quality, differential diagnosis definition and outcome reporting.
Generating evidence on treatment strategies

Studies on the management of HG have focused primarily on pharmaceutical interventions and complementary medicine, while dietary modifications are frequently recommended but have not been subjected to systematic evaluation of efficacy.\textsuperscript{10} We therefore undertook the MOTHER trial, in which we assessed the effectiveness of early enteral tube feeding as a first line treatment option for HG. Tube feeding did not affect primary or secondary outcomes. Participating women poorly tolerated enteral tube feeding, which may have limited contrast between treatment strategies in terms of caloric intake. Furthermore, food intake likely varies substantially depending on the symptom severity and persistence. In the absence of diagnostic criteria and predictors of prolonged disease, the MOTHER trial pragmatically included all women with HG in need for treatment in hospital, which in conjunction with the limited sample size, affected our ability to distinguish treatment effects in mild cases compared to the effects in severe cases with prolonged symptoms. If, in the future, it becomes possible to identify women who are likely to suffer from prolonged symptoms, for example through identification of \textit{H pylori} infection\textsuperscript{12} or HG-associated genes,\textsuperscript{13} it would be interesting to study the effectiveness of a targeted nutritional intervention in these women.

While the MOTHER trial was unable to show effects on short-term outcomes, we found that weight loss in early pregnancy, but not hospital admission for HG, was associated with slightly increased diastolic blood pressure in childhood. Early increases in blood pressure are known to track into adulthood and may predict later development of hypertension.\textsuperscript{14} These findings suggest that more severe HG, in this case determined by weight loss, could have long-term consequences. Although long-term follow up of perinatal trials is challenging for numerous reasons,\textsuperscript{15} effort should be made to follow-up offspring born to mothers with HG, either through prospective cohorts or trials such as the MOTHER trial. This is important because long-term follow up of offspring following obstetric interventions has the potential to reveal both negative\textsuperscript{16} and positive\textsuperscript{17} treatment effects, even when short-term benefits are lacking.

Improving quality of evidence

Both previously conducted studies and research projects presented in this thesis are affected by the lack of consensus on a HG definition and outcomes that are relevant to all stakeholders. Commonly, research projects are designed without consulting patients, while patient and public involvement in studies has been shown to positively impact research question relevance, study design, participant recruitment and adherence to a study and interpretation and communication of results.\textsuperscript{18} The Outcome
Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) working group was the first to recognise the value of consensus conferences to develop core outcome sets and active engagement of patients. Since 2010, the principles of core outcome set development are further collated by the Core Outcome Measures in Effectiveness Trials (COMET) initiative (www.comet-initiative.org) and in 2014 the CoRe Outcomes in Women’s and Newborn health (CROWN) initiative was established. This initiative, led by numerous leading journal editors, promotes core outcome set development in women’s health research to improve data synthesis and implementation of evidence in clinical guidelines and maternity care. Meanwhile, core outcome sets for epilepsy in pregnancy, preterm birth and maternity care have been developed and more projects registered in the COMET database are ongoing (www.comet-initiative.org).

In line with CROWN recommendations, we are now conducting the Definition and Core Outcomes for Hyperemesis Gravidarum (DCOHG) project (www.comet-initiative.org/studies/details/805). This project engages multiple stakeholders including researchers, healthcare professionals, journal editors and patients from around the globe, to develop a consensus statement on HG definition and a minimum set of outcomes that should preferably be measured in all trials, while researchers continue to explore other outcomes depending on their hypothesis. To reach consensus, a modified Delphi method is used, which includes several survey rounds followed by a consensus meeting. Besides consensus on which items are most relevant for HG definition and what outcomes should be measured, further agreement on how to measure these items and outcomes is needed, as the number of measurement instruments currently used largely exceeds the number of definition items and outcomes (chapter 9). Guidelines on the selection of measurement instruments have been developed.

A consensus statement on HG definition and core outcomes is only meaningful if it results in uptake and implementation by researchers and guideline developers. This may be accomplished through participation in a consensus project, through publication of results, encouragement of authors by CROWN editors to make use of this consensus definition and core outcome set and through international meetings. Recently, HG researchers and patient organisations recognised the value of collaboration in bringing HG research and patient care forward, which resulted in the foundation of the International Colloquium on Hyperemesis Gravidarum (ICHG; www.hgconference.org). This platform may bring stakeholders together to prioritize research questions and sharing study protocols.

Although bringing stakeholders together is a first step, more is needed to enable evidence based medical care for HG patients. For instance, the quality of existing studies on HG is generally low. Enhancing the use of reporting guidelines, such as
promoted by the Enhancing QUAlity and Transparency Of health Research (EQUATOR) network, is needed to improve the quality of future studies and publications and to limit wastage of human and financial resources (www.equator-network.org). This is particularly important because HG research is often performed with no or limited budget.

**Implementing evidence in clinical guidelines and clinical practice**

To reach healthcare professionals, uptake of research evidence in clinical guidelines is needed. Recently, the American (ACOG) and British (RCOG) colleges of obstetricians and gynaecologists have both published a practice guideline on the management of HG,\(^{27, 28}\) but in the Netherlands no national guideline exists. Since applicability of guidelines regarding health care system, system of remuneration and distribution of facilities all determine adherence to guidelines,\(^{29}\) adaptation of existing guidelines (like the ACOG or RCOG guideline) to a national level could increase implementation of research evidence into clinical practice. Adherence to guidelines is also affected by barriers to change. These can be present at individual, team and hospital levels and will amongst others depend on attitude (e.g. urgency to act) and prevailing opinion (e.g. common practice). Identification of these barriers, for example through focus groups, is needed to develop targeted strategies to bridge the gap between best practice and actual care for HG patients.\(^{30}\)

**Incorporating patient preferences and values**

Contemporary EBM practice also incorporate patient’s perspectives, experiences and choices. This shift towards patient-centred medicine implicates a greater role for patient preferences.\(^{31}\) Currently, systematic evidence on HG patient preferences is lacking, but exemplary are quotes from a report by the British HG patient organisation,\(^{32}\) which states that patients have decided to terminate their pregnancy because their health care provider was not willing to prescribe antiemetic medication of which teratogenic effects could not be ruled out. Thus, understanding patient trade-offs is important when it comes to treatment preferences and compliance, trial participation and identification of potential treatment strategies that need further investigation.

To conclude, barriers and challenges in HG research are numerous, but not impossible to overcome. With the initiation of international collaboration projects involving researchers, healthcare professionals and patients, the momentum is there to bring the principles of evidence based medicine to HG research and ultimately improve care for mothers and children affected by HG.
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