Hyperemesis gravidarum

Definition, treatment, prognosis and offspring outcome

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1 General introduction and outline of this thesis
Hyperemesis gravidarum: historical aspects

Nausea and vomiting during pregnancy are symptoms that have been known for millennia and are considered part of a normal, healthy pregnancy. The oldest description about vomiting as a symptom of early pregnancy dates as far back as 2000 BC, in the ancient Kahun Papyrus, the oldest medical text found in Egypt.\(^1\) The link between the degree of nausea and vomiting and female gender was probably already described by Hippocrates (460-377 BC), who said that a woman pregnant with a female foetus would have an unhealthy pale appearance.\(^2\)

The first more detailed description about nausea and vomiting in pregnancy was from Soranus (98-138 AD), a physician who practiced medicine in Rome around 120 AD. Soranus described how the sickness of pregnancy commences around the fortieth day of pregnancy and persists for maximum 4 months. He also described that some women are affected with vomiting at intervals, dizziness, headache, pallor, the appearance of undernourishment and that some may display jaundice.\(^3\) The latter might be the first description in literature of what later would be referred to as 'hyperemesis gravidarum' (HG), an extreme form of nausea and vomiting in pregnancy. In 1706 the first death of a pregnant woman associated with vomiting was reported.\(^3\) History’s most famous fatal case of HG is probably the English novelist Charlotte Brontë (1816-1855), author of Jane Eyre. Her condition was described as ‘a neurosis and rejection of her pregnancy and femininity’, although an analysis of Brontë’s last month’s casts doubts about whether she really was pregnant.\(^4\) There were indications that tuberculosis with secondary Addison’s disease was more likely to be the cause of her death. An explanation for here falsely stated cause of death may be that many found it to be unacceptable that a literary work of such magnitude could be written by a woman. The argument that this was not the work of a genius but simply the description of a neurotic woman may have been more comforting.\(^4\) What really caused Brontë’s death will remain unknown, but unfortunately she was not the last woman whose symptoms were ascribed to neurosis or hysteria. Although very early theories about the aetiology of nausea and vomiting in pregnancy suggested a neurological connection between abdominal organs and the growing uterus, by the late 19\(^{th}\) century intrapsychic theories about the cause of the condition took the upper hand.\(^5\) In 1934, Atlee suggested that severe nausea and vomiting in pregnancy may be a ‘distorted attempt on the part of the woman’s unconscious mind to rid herself of her foetus’\(^6\) and in 1968, Fairweather suggested that vomiting in pregnancy was associated with hysterical personality types and lower intelligence.\(^3\)

There has been a renewed interest in the aetiology of nausea and vomiting in pregnancy since the 1980s and original theories have been developed and refined. Since then, the aetiology of HG has been considered multifactorial with proposed underlying causes related to abnormal placental growth, maternal endocrine function and gastrointestinal function.\(^7\)
Definition and diagnosis

The first clinical description of different stages of vomiting during pregnancy dates back to 1852 when A.P. Dubois, a French obstetrician, divided the syndrome in 3 stages:

First, constant vomiting associated with considerable emaciation and frequently with troublesome dribbling of saliva, at the same time urine becomes scanty and highly coloured and the pulse somewhat accelerated. Second, the vomiting becomes still more severe, emaciation more pronounced and the breath assumes a peculiar acid and fetid odour. The pulse increases in frequency and there may be a slight rise in temperature. Third, there is an apparent amelioration of symptoms for a short time during which vomiting sometimes ceases and the patient passes into delirium or a torpid condition and dies in coma or convulsions.\(^3,^8,^9\)

It is not entirely clear when the term ‘hyperemesis gravidarum’ was first used, but one of the first written accounts of the term is probably from 1898, when C.S. Bacon, an American obstetrician linked the term to the classifications of Dubois.\(^10\) A panel appointed by the American Council on Pharmacy and Chemistry in 1956 defined HG as “intractable vomiting and disturbed nutrition, such as alteration of electrolyte balance, loss of weight of 5% or more, ketosis and acetonuria, with ultimate neurological disturbances, liver damage, retinal haemorrhage and renal damage”.\(^11\) However, Fairweather emphasises in his paper from 1968 that it is difficult to find a definition of HG in any obstetric textbook, as it is not easy to distinguish between physiological NVP and HG.\(^3\)

HG was for the first time included in the 6\(^{th}\) revision of the international classification of disease (ICD). In ICD-6 (1949-1958) and ICD-7 (1955-1968) HG symptoms were not specified. In ICD-8 (1968-1979) HG was described as “Hyperemesis with mention of neuritis or without mention of neuritis”. ICD-9 (1979-1993) described HG as “excessive vomiting in pregnancy” and distinguished between mild HG and HG; with and without metabolic disturbances. ICD-10 (1993-2018) added to ICD 9 that symptoms should have started before the 22\(^{nd}\) week of gestation. In June 2018 ICD-11 was released differentiating between mild or unspecified HG “vomiting occurring during pregnancy responsive to dietary modification and antiemetics” and HG with metabolic disturbance “vomiting in pregnancy, not responsive to dietary modification and antiemetic treatment and associated with electrolyte disturbances and acid-base imbalance”.

In practice, HG is currently a clinical diagnosis made after other causes of nausea and vomiting have been excluded. Commonly used criteria include severe nausea and vomiting, weight loss, dehydration, electrolyte imbalances and the need for hospitalisation.\(^12,^13\)
Impact of hyperemesis gravidarum for mother and child

Women with HG are at risk of malnutrition. A rare but potentially life-threatening complication is Wernicke encephalopathy, caused by acute thiamine deficiency. In addition to physical complications, HG can have profound impact on maternal wellbeing and quality of life. There is evidence that these consequences persists beyond pregnancy with reports of post-traumatic stress symptoms in up to 20% of women with HG.

There are indications that HG may lead to adverse perinatal outcomes, especially among patients with poor nutritional status and symptoms that persist in the second trimester. Research assessing possible long-term consequences of HG for the offspring are limited. Two studies reported an association between prenatal exposure to HG and neurodevelopmental delay and an increased risk of psychological and behavioural disorders in the offspring. Another study showed that insulin sensitivity in prepubertal offspring of mothers with HG is decreased, which suggests an increased risk of cardiometabolic disease later in life.

Treatment options

There is a lack of robust evidence for the efficacy of treatment and management of HG and currently, there is no national guideline in the Netherlands for HG care. Hospital admission with intravenous rehydration and antiemetic medication are often applied. Two recent studies from the UK showed that rehydration therapy in day care setting is as effective as rehydration therapy in inpatient management. There is evidence of safety for the most frequently used antiemetics, including metoclopramide and antihistamines. Another anti-emetic that can be effective in the treatment of HG is ondansetron. Although most studies found no association between maternal ondansetron use in pregnancy and congenital anomalies, there have been indications for a small increase in congenital heart disease and cleft palate. Nonetheless, the Royal College of Obstetrics and Gynaecology (RCOG) latest guideline considers ondansetron safe and recommends its use after the first trimester. Dietary advice is sometimes given during HG treatment but is not evidence based. Nutritional intervention studies are rare. Other management options for HG that have been explored are mindfulness-based cognitive therapy, acupressure and acupuncture, showing conflicting results. All in all, there are some treatment options available for HG, but there is a paucity of high quality research and evidence.
Aims and outline of this thesis

So far, we have given a historical perspective and we have briefly summarised the current state of affairs concerning knowledge, research and treatment options for HG. Although we have illustrated that the perspective of the disease has improved over the past decades, there are still several big hurdles in HG research and patient care. For one, the aetiology of HG is poorly understood and tools to diagnose or predict disease severity are lacking. This hampers identification of women at risk for a severe disease course of HG. Secondly, there is an absence of high-quality evidence on the effective treatment of HG. This negatively affects patient care. Third, research assessing possible long-term consequences of HG for the offspring are limited. Therefore, potential harm for the offspring may not be addressed in current clinical practice. Lastly, there is no consensus on the definition of HG, or on outcomes that should be reported in trials. This hampers meaningful aggregation of trial results in meta-analysis and implementation of evidence in guidelines. In this thesis, we will address the identified problems by studying the following:

Part I studies potential biomarkers and determinants of HG disease severity. In chapter 2 we evaluate the use of ketonuria as a HG disease severity marker. In chapter 3 we explore the association between patient characteristics and clinical features and several measures of HG disease severity. Part II addresses treatment options for HG. In chapter 4 we give an overview of the current knowledge and treatment options available and we explain how the Dutch patient association can contribute in patientcare. In chapter 5 we describe the results of a randomised controlled trial (Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding), in which we assess the effectiveness of early enteral tube feeding for maternal and offspring outcomes. Part III explores whether HG is associated with long-term health effects of the offspring. In chapter 6 we report on the association between maternal hospital admission for HG and markers of cardiometabolic health, including body mass index, blood pressure, glucose and lipid levels, in their 16-year old offspring. In chapter 7 we report on the association between maternal hospital admission for HG and several measures of psycho-behavioural development in their offspring at 8 and 16 years. Part IV addresses the lack of an international consensus for HG definition. In chapter 8 we describe how the lack of a consensus of the definition of HG hampers research and we give an overview of the variation in HG definition and outcome reporting in randomised controlled trials.
Chapter 1

References


Introduction


