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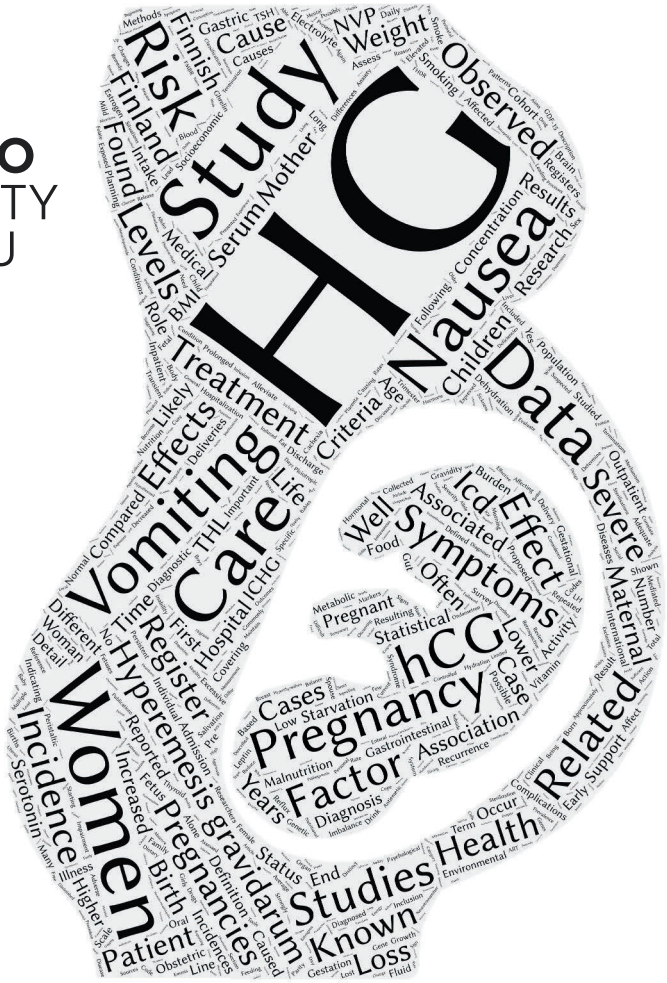

HYPEREMESIS GRAVIDARUM

Incidence, recurrence, hospitalizations, outpatient care and effect on family planning

Miina Nurmi

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1653 | MEDICA – ODONTOLOGICA | TURKU 2022

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“Everyone has their own number
in the system that we operate under
We're moving to a situation
where your lives exist as information”
Neil Tennant, Integral (2006)

To my loved ones, particularly Tuomas, Minea and Volter,
and all fellow number and information enthusiasts.

UNIVERSITY OF TURKU
Faculty of Medicine
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ABSTRACT

Hyperemesis gravidarum (HG), severe and intractable vomiting of pregnancy, affects approximately 1% of pregnancies. The symptoms prevent sufficient intake of food and liquids, causing suffering and requiring treatment such as intravenous hydration, nutrition or medication. The present thesis aimed at elucidating various aspects of HG in Finland: incidence, outpatient visits and hospitalizations, readmissions, and recurrence, as well as effects on family planning and associations between maternal, environmental, and pregnancy-related factors and HG.

The data were collected from health care registers: the Hospital Discharge Register, the Medical Birth Register, the Register of Induced Abortions, and the Sterilization Register. Women with deliveries in 2004–2017 were included in the study. 9,315 women diagnosed with HG in any pregnancy were chosen as case women, and 428,150 women never diagnosed with HG as reference women.

Incidence of HG was 1.3%. Readmission rate due to HG was 60% (both outpatient visits and hospitalizations), and rehospitalization rate was 17%. HG recurred in 24% of pregnancies following an initial HG pregnancy. Obesity, living in municipalities with higher population count, assisted reproductive technology (ART), multiple gestation, and female sex of the fetus were associated with higher risk of HG, whereas smoking was associated with a lower risk. Higher parity, multiple gestation, and female sex of the fetus were associated with higher risk of readmission, while higher maternal age, BMI $\geq$ 35, smoking and ART were associated with lower risk. Female fetus was associated with higher risk of recurring HG, and smoking was associated with lower risk of recurrence. Women with HG had more pregnancy terminations and sterilizations compared to women never diagnosed with HG, but HG did not reduce the overall number of deliveries.

HG is relatively rare, whereas common nausea and vomiting during pregnancy affects the majority of pregnancies, and interview studies have described how it has frustrated and discouraged women with HG if their symptoms have been misinterpreted as “normal”, leading to insufficient recognition of HG and delayed access to care. The results of the present thesis highlight the importance of identifying and treating the HG efficiently.

KEYWORDS: Hyperemesis gravidarum; nausea; vomiting; pregnancy; incidence; recurrence; admission; readmission; family planning

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TIIVISTELMÄ

Hyperemesis gravidarum (HG) tarkoittaa vakavaa raskauspahoinvointia, jota esiintyy noin yhdessä sadasta raskaudesta. HG-oireet aiheuttavat kärsimystä, voivat estää riittävän syömisen ja juomisen, ja tila vaatii usein suonensisäistä nesteytystä ja ravitsemusta sekä lääkehoitoa. Tässä väitöstutkimuksessa selvitettiin HG:n ilmaantuvuutta, toistuvaa hoidon tarvetta, HG:n toistumista seuraavissa raskauksissa, vaikutusta perhesuunnitteluun sekä erilaisten taustatekijöiden ja HG:n välisiä yhteyksiä.

Tutkimusaineisto koottiin Terveyden ja hyvinvoinnin laitoksen ylläpitämistä Hoitoilmoitusrekisteristä, Syntyneiden lasten rekisteristä, Raskaudenkeskeytysrekisteristä ja Steriloimisrekisteristä. Tutkimukseen valittiin naiset, joilla oli v. 2004–2017 vähintään yksi synnytys: 9 315 naista, joilla oli HG-diagnoosi vähintään yhdessä raskaudessa sekä verrokkihenkilöiksi 428 150 naista, joilla ei ollut HG-diagnoosia yhdessäkään raskaudessa.

HG:n ilmaantuvuus oli 1,3 %. Näistä raskauksista 60 % vaati useamman kuin yhden poliklinikkakäynnin tai sairaalahoitojakson HG:n vuoksi, ja 17 %:ssa raskauksista useamman sairaalahoitojakson. HG toistui 24 %:ssa aiempaa HG-raskautta seuranneista raskauksista. Lihavuus, kotikunnan korkea asukasluku, hedelmöityshoidot, monisikiöraskaus ja tyttösikiö olivat yhteydessä korkeampaan ja tupakointi matalampaan HG:n riskiin. Uudelleensynnyttäjyys, monikkoraskaus ja tyttösikiö liittyivät suurempaan hoidon tarpeeseen ja korkeampi ikä, tupakointi ja hedelmöityshoidot pienempään. Tyttösikiö oli yhteydessä suurempaan ja tupakointi pienempään HG:n toistumisriskiin. HG:n kokeneilla naisilla oli enemmän raskaudenkeskeytyksiä ja sterilisaatioita kuin verrokkihenkilöillä, mutta HG ei vähentänyt synnytysten määriä.

Normaaliin raskauspahoinvointiin verrattuna HG on melko harvinainen ja huonosti tunnettu tila, ja HG-potilaat ovat kuvanneet, miten turhauttavaa ja masentavaa on, jos hyperemeesiä luullaan tavalliseksi pahoinvoinniksi. HG:n tunnistaminen on tärkeää sekä oikean diagnoosin että hoitoon pääsyn ja hoidon onnistumisen varmistamiseksi.

AVAINSANAT: Hyperemesis gravidarum; pahoinvointi; oksentelu; raskaus; ilmaantuvuus; toistuminen; sairaalahoito; toistuva sairaalahoito; perhesuunnittelu

Table of Contents

Abbreviations

5-HT	5-hydroxytryptamine; serotonin
ANOVA	analysis of variance
ART	assisted reproductive technology
BMI	body mass index
CI	confidence interval
ECG	electrocardiogram
FHDR	Finnish hospital discharge register
FMBR	Finnish medical birth register
H2S	hydrogen sulphide
hCG	human chorionic gonadotropin
H. pylori	helicobacter pylori
HG	hyperemesis gravidarum
ICD-10	international classification of diseases, 10th revision
ICHG	International Colloquium on Hyperemesis Gravidarum
IRR	incidence rate ratio
NVP	nausea and vomiting of pregnancy
NVPQoL	nausea and vomiting in pregnancy specific quality of life questionnaire
OR	odds ratio
QoL	quality of life
PUQE	pregnancy-specific quantification of emesis questionnaire
RR	relative risk
SES	socioeconomic status
SGA	small for gestational age
STROBE	strengthening the reporting of observational studies in epidemiology
TSH	thyroid stimulating hormone
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Nurmi Miina, Rautava Päivi, Gissler Mika, Vahlberg Tero & Polo-Kantola Päivi. Incidence and risk factors of hyperemesis gravidarum: A national register-based study in Finland, 2005–2017. Acta Obstetricia et Gynecologica Scandinavica, 2020; 99(8):1003–1013.

II Nurmi Miina, Rautava Päivi, Gissler Mika, Vahlberg Tero & Polo-Kantola Päivi. Readmissions due to Hyperemesis Gravidarum : a nation-wide Finnish register study. Archives of Gynecology and Obstetrics. Online ahead of print. Doi: https://doi.org/10.1007/s00404-022-06448-w

III Nurmi Miina, Rautava Päivi, Gissler Mika, Vahlberg Tero & Polo-Kantola Päivi. Recurrence patterns of hyperemesis gravidarum. American Journal of Obstetrics and Gynecology, 2018; 219:469.e1–10.

IV Nurmi Miina, Rautava Päivi, Gissler Mika, Vahlberg Tero & Polo-Kantola Päivi. Hyperemesis gravidarum and family planning. Manuscript.

1 Introduction

"Next time we meet, it will certainly have passed", I remember having heard quite a few times while expecting my first child. Like many, I had heard about morning sickness, but had not expected it to last all day and for such a long time. The maternity health center nurses' attempts to assure that it will soon pass made me wonder whether it was normal or not to feel sick past the first trimester. I was also pondering whether more efficient treatment options in addition to eating dry crackers in the morning existed.

Curious as I am, I decided to find out more, but as it was difficult to concentrate on anything while nauseous most of the time, it was not until towards the end of the pregnancy that I was able to properly have a look at some studies about nausea and vomiting of pregnancy (NVP). Some studies! It had been studied more extensively than I had expected.

I realized that my symptoms, as annoying as they were, were actually quite mild – it could have been a great deal worse. Up to 91% of pregnant women experience NVP to some degree, whereas approximately 1% suffer from hyperemesis gravidarum (HG), intractable, severe nausea and vomiting often requiring hospital care (Koot et al., 2018; Verberg et al., 2005).

Despite its relative rarity, HG causes a considerable burden of illness: it is the most common cause of hospitalization in the first trimester of pregnancy in pregnancies resulting in delivery (Gazmararian et al., 2002), and rehospitalization rates of 13–34% have been reported (Chraibi et al., 2015; Derbent et al., 2011; Koot et al., 2020; Sharp et al., 2016; Tan et al., 2006).

The cause of NVP and HG remains unknown, although several associative factors have been studied and identified. Increased risk of HG has been associated with e.g. young maternal age (Fell et al., 2006), under- or overweight (Matsuo et al., 2007; Vikanes et al., 2010), assisted reproductive technology (ART) (Roseboom et al., 2011), multiple pregnancy (Fell et al., 2006), and female fetus (Fiaschi et al., 2016; Peled et al., 2013; Vikanes et al., 2008). Smoking is associated with lower risk of HG, possibly due to its damaging effect on the placenta (Fell et al., 2006; Vikanes et al., 2010). Results regarding the effect of previous pregnancies have been inconclusive: in some studies, women expecting their first child have been found to

be at a higher risk (Fell et al., 2006; Fiaschi et al., 2016; Roseboom et al., 2011), while other studies have found opposite results (Vikanes et al., 2013; Vilming et al., 2001), or no association at all (Bailit, 2005; Matsuo et al., 2007). The etiology is thus likely to be multifactorial, and the risk in any individual pregnancy appears to be affected by each woman's particular situation.

Information about NVP and HG can mostly be found in research literature in English. When feeling sick, it may not be easy to follow scientific text in a foreign language, and some data sources are not freely available outside the academia. To increase accessibility to evidence-based data about NVP and HG to both pregnant women and health care professionals, I began condensing research results about NVP and HG into a web site in Finnish (Nurmi, 2020), conducted a survey regarding pregnant women's and maternity health care nurses' need of knowledge about NVP and HG (Nurmi, 2011), and another survey examining health literacy (Nurmi, 2014).

The results indicated a wide knowledge gap, and a larger scientific study about NVP and HG was initiated with other researchers joining the research group. This thesis focuses on HG, while other group members are working on NVP data, with a common goal of providing knowledge and tools for the health care system to promptly and efficiently respond to the needs of pregnant women suffering from NVP or HG. In addition to studying the incidence of HG in Finland and factors affecting the risk of HG, two research topics emerged from messages I have received from women and their partners contacting me through the NVP/HG web site: recurrence of HG in following pregnancies and the effect of HG on family planning. One of the most common questions of women who have experienced HG is "Will it happen again?" Despite its clinical importance, the likelihood of recurrence of HG in subsequent pregnancies is not well known. Reported recurrence rates vary between 15% and 81%, survey-based studies generally yielding higher rates compared to register-based studies (Dean et al., 2019; Fejzo et al., 2011; Fejzo et al., 2012; Fiaschi et al., 2016; Trogstad et al., 2005).

The most unexpected messages I received concerned pregnancy terminations due to HG: in some cases, planned and wanted pregnancies have had to be terminated due to HG, even in Finland, and even in the 21st century. In international questionnaire and interview studies, women with HG have expressed avoiding further pregnancies, considering pregnancy termination, or having terminated a hyperemetic pregnancy (Fejzo et al., 2011; Havnen et al., 2019).

To answer these questions and to raise awareness about NVP and HG, the studies presented here have been conducted. Thus, one thing leading to another, my initial "having a look at some studies" has culminated in this thesis.

2 Review of the Literature

The earliest known description of nausea and vomiting in early pregnancy is found in an Egyptian papyrus dated to approximately 2000 B.C., now stored in The Petrie Museum of Egyptian Archaeology in London (Fairweather, 1968). In the 5th century B.C., Hippocrates mentioned nausea as a sign of pregnancy:

> "If a woman's courses be suppressed, and neither rigor nor fever has followed, but she has been affected with nausea, you may reckon her to be with child." (Hippocrates/The Internet Classics Archive, 2009)

The condition was described in some more detail by Soranus in the 2nd century A.D. in his writings on gynecology (Temkin et al., 1991). Although Soranus apparently did not consider nausea and vomiting to constitute a distinct syndrome, but rather referred to these symptoms in the context of his lengthy description of pica, his portrayal neatly illustrates some symptoms of NVP, and even resembles symptoms of HG in some respects:

> "Some women are also affected with vomiting at intervals or at each meal, or with a feeling of heaviness, dizziness, headache, discomfort together with an abundance of raw humors, pallor, the appearance of undernourishment, constipation; some also have gastric distention, or pain in the thorax, the same persons sometimes also show very slight fever and swelling up of the breasts (the swollen vessels are greenish in some, livid in others) and some display jaundice." (Soranus/Temkin et al., 1991)

The severe form of nausea and vomiting of pregnancy was not called "hyperemesis gravidarum" until towards the end of the 19th century A.D., when the term began to appear in medical articles and books (Das, 1898; Fruitnight, 1890; Shrady et al., 1888).

From 1898 to 2020, 2,111 publications identified with the search phrase "hyperemesis gravidarum" were indexed in the medical literature database of the US

National Library of Medicine of the National Institute of Health (PubMed, 2021) (**Figure 1**).

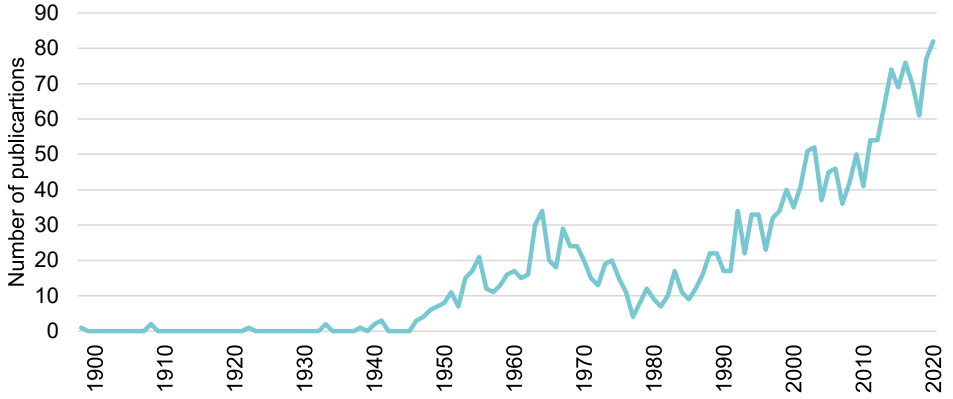

Figure 1. The number of publications containing the phrase "hyperemesis gravidarum" indexed in the US National Library of Medicine, 1898–2020.

In the 1950's, interest in medical treatment of HG began to increase, reflected in the number of publications. However, as one commonly prescribed antiemetic drug, thalidomide, was observed to cause malformations in the fetus (McBride, 1961; Lenz et al., 1962; Vargesson, 2015), both doctors and pregnant women became wary about using any medication during pregnancy, and HG research was stalled for some time before increasing again. A recent survey demonstrated that even though awareness about the thalidomide tragedy has diminished, women remain cautious towards drug use during pregnancy (Petersen et al., 2015).

Despite these numerous studies, neither the cause of HG, nor curative treatment for HG has been found. The etiology is likely to be multifactorial, and hence it is unlikely that a one-for-all-treatment will be found, and many current studies aim at accumulating knowledge of factors affecting the risk of HG and characteristics of HG sufferers, to eventually enable better targeting of treatment.

2.1 Definition, diagnosis and treatment of HG

Variation in HG definition is considerable, and this has led to difficulties in comparing results of different studies (Grooten et al., 2016; Koot et al., 2018). Different criteria are applied depending on e.g. study settings and data availability.

2.1.1 Definition and diagnosis

As NVP and HG are not clearly delimited but occur as a spectrum, distinction between the conditions is not unambiguous, hampering clarity in definition and diagnosis of both NVP and HG. In practice, the demarcation is based on symptom severity: universally accepted diagnostic criteria for HG remain to be defined (Grooten et al., 2016; Koot et al., 2018) and the criteria may differ according to local clinical practices. Most commonly, the criteria include persistent vomiting not attributable to other causes, signs of dehydration and/or starvation, and weight loss of at least 5% of prepregnancy weight (American College of Obstetrics and Gynecology, 2018; Goodwin, 2008; Laitinen et al., 2019). In association with the International Colloquium on Hyperemesis Gravidarum (ICHG), an international consensus definition of HG for use in clinical trials has been developed as a result of cooperation between HG researchers, HG patient representatives, health care personnel and other stakeholders (Jansen et al., 2021).

In 2019, version 1.0 of the consensus definition was presented in the Third ICHG, containing the following criteria:

- Pregnant woman
- Other causes of nausea and vomiting have been excluded
- Beginning of symptoms in early pregnancy
- Symptoms: Nausea and vomiting (at least one of these severe)
- Inability to eat/drink normally
- Strong effect on daily activity
- Signs of dehydration

The consensus definition mentioned above was published in print in 2021 and named the Windsor definition of HG (Jansen et al., 2021), consisting of the final criteria:

- Start of symptoms in early pregnancy (before 16 weeks gestational age)
- Nausea and vomiting, at least one of which severe
- Inability to eat and/or drink normally
- Strongly limits daily living activities

Signs of dehydration were not included in the final definition but were deemed contributory (Jansen et al., 2021).

The definition is primarily intended for clinical trials, and the specificity of certain of the criteria included in the definition limit its practicability. In studies based on medical records or registers, the definition cannot be implemented, but in prospective studies, the different aspects of the definition can be taken into account

in the research plan. Specific variables or measurement tools regarding each part of the definition have not been determined, allowing researchers freedom to choose the best methods applicable in each study.

In Finland, HG is currently diagnosed according to the 10th release of the International classification of diseases (ICD-10) (**Table 1**, **Table 2**) (World Health Organization, 2012; World Health Organization, 2016; World Health Organization, 2020 a). HG is a diagnosis of exclusion: other conditions which can cause nausea or vomiting, such as gastrointestinal or genitourinary infections, as well as metabolic and neurologic disorders are to be considered (American College of Obstetrics and Gynecology, 2018; Goodwin, 2008; Laitinen et al., 2019).

Although primarily intended as clinical tools rather than definitions, the disease descriptions are often the only resource for defining HG cases in register research. ICD codes related to HG in the 10th release of the ICD (in effect during the study period of the present study, 2004–2017) are presented in **Table 1**, and the 11th release (the most recent version, in effect since 2018 and to be introduced in Finland as of 2023–2026) in **Table 2**.

Table 1. HG diagnostic codes in the 10th release of the international classification of diseases (ICD-10).

O21, Excessive vomiting in pregnancy

O21.0	Mild hyperemesis gravidarum Hyperemesis gravidarum, mild or unspecified, starting before the end of the 22nd week of gestation
O21.1	Hyperemesis gravidarum with metabolic disturbance Hyperemesis gravidarum, starting before the end of the 22nd week of gestation, with metabolic disturbance such as: carbohydrate depletion dehydration electrolyte imbalance
O21.2	Late vomiting of pregnancy Excessive vomiting starting after 22 completed weeks of gestation
O21.8	Other vomiting complicating pregnancy Vomiting due to diseases classified elsewhere, complicating pregnancy Use additional code, if desired, to identify cause.
O21.9	Vomiting of pregnancy, unspecified

Table 2. HG diagnostic codes in the 11th release of the international classification of diseases (ICD-11).

JA60, Excessive vomiting in pregnancy

JA60.0	Mild hyperemesis gravidarum Description: Vomiting occurring during pregnancy responsive to dietary modification and antiemetic treatment Inclusions: Hyperemesis gravidarum, mild or unspecified, starting before the end of the 22nd week of gestation Exclusions: Hyperemesis gravidarum with metabolic disturbance (JA60.1)
JA60.1	Hyperemesis gravidarum with metabolic disturbance Description: Vomiting in pregnancy, not responsive to dietary modification and antiemetic treatment and associated with electrolyte disturbances and acid-base imbalance
JA60.2	Late vomiting of pregnancy Description: Vomiting occurring after 16 weeks gestation Inclusions: Excessive vomiting starting after 22 completed weeks of gestation
JA60.Y	Other specified excessive vomiting in pregnancy This category is an 'other specified' residual category
JA60.Z	Excessive vomiting in pregnancy, unspecified This category is an 'unspecified' residual category

Examples of definition or criteria of HG in different publications are presented in **Table 3**. Some authors cite symptoms or other specific criteria such as laboratory measurements, while others refer to e.g. local hospital admission criteria or the ICD-10 classification system.

Table 3. Examples of definition or criteria of HG.

Reference	Definition of HG	Study design
Fairweather, 1968	“Vomiting occurring before 20 weeks’ gestation and sufficiently severe to require hospital admission.”	Review
Chin, 1989	“Vomiting of such degree as to require the patient’s admission to hospital, but unassociated with underlying diseases such as appendicitis, pyelitis, etc.”	Prospective cohort study
Nelson-Piercy et al., 2001	“ - - persistent nausea and vomiting of such severity that the woman is unable to maintain adequate hydration, electrolyte balance or nutritional status”	Randomized control trial
Verberg et al., 2005	“- - nausea and vomiting in pregnancy typically in the first trimester resulting in dehydration and ketonuria severe enough to justify hospital admission and require i.v. fluid therapy, after exclusion of any other causes of vomiting”	Review

Peled et al., 2013	"- - first- or early second-trimester pregnant women with unrelenting, excessive pregnancy-related nausea and/or vomiting that prevents adequate intake of food and fluids with or without abnormal laboratory results such as ketonuria or electrolytes disturbance are admitted for hospitalization and defined as having [HG]"	Retrospective cohort study
Vandraas et al., 2013	"HG was defined according to International Classification of Diseases, 8th revision (ICD-8) diagnosis codes 638.0 and 638.9 during 1967–98, and ICD-10 diagnosis codes 021.0, 021.1 and 021.9 during 1999–2009"	Retrospective population-based cohort study
Niemeijer et al., 2014	"We defined HG as any combination of nausea, vomiting, dehydration, weight loss, or hospitalization for nausea and/or vomiting in pregnancy, in the absence of any other obvious cause for these complaints."	Review
Fiaschi et al., 2016	"A pregnancy was considered to be affected by HG if at least one admission with primary diagnosis [ICD-10] for HG was recorded during the gestational period excluding the delivery admission"	Retrospective population-based cohort study
Mitchell-Jones et al., 2017	"As there is no standardised definition of HG, we assessed the inclusion criteria for each paper looking for the use of objective diagnostic criteria such as a symptom scoring system, e.g. PUQE (Pregnancy Unique Quantification of Emesis, weight loss or ketonuria. Admission to hospital alone was not considered adequate case definition unless specific admission criteria were given."	Review
Havnen et al., 2019	"HG was defined as either a medical diagnosis of HG or at least two out of three clinical features of HG: (1) weight loss exceeding 5% of the pre-pregnancy weight; and/or (2) ketones on a urine analysis; and/or (3) dehydration and/or an electrolyte imbalance."	Cross-sectional survey
Koot et al., 2020	Severe form of nausea and vomiting in pregnancy that can lead to dehydration, electrolyte disturbances or significant weight loss, necessitating hospital admission	Prospective cohort study
Jansen et al., 2021	Start of symptoms in early pregnancy (before 16 weeks gestational age); Nausea and vomiting, at least one of which severe; Inability to eat and/or drink normally; Strongly limits daily living activities	Survey; international consensus study

In the present study, HG cases were defined by presence of HG diagnosis in the Finnish Hospital Discharge Register (FHDR) according to the ICD-10 descriptions. The inclusion process is described in detail in the Materials and Methods chapter.

2.1.2 Symptoms

Symptoms of HG include persistent nausea and vomiting, inability to tolerate oral food or liquids, ptyalism (excessive salivation), and general impairment in daily life

functioning (Bronshtein et al., 2018; Fejzo et al., 2019; Heitmann et al., 2017; Suzuki et al., 2009). Symptoms of gastrointestinal reflux disease such as heartburn, indigestion and regurgitation often occur in association with HG, as the decreased tone of the lower esophageal sphincter and slower gastrointestinal transit time induced by hormonal changes may contribute to both HG and gastrointestinal reflux (Clark et al., 2014).

Physiology of nausea and vomiting is known to some extent. In the central nervous system, a brain region called area postrema located at the base of the fourth ventricle outside of the blood-brain barrier and thus able to monitor signalling molecules and harmful substances in the blood, is capable of initiating signalling pathways leading to nausea and vomiting (Hornby, 2001; Price et al., 2008). Nerves of the enteric nervous system detecting intestinal and gastric status are also connected to the central nervous system and can mediate signals of nausea by neurotransmitters such as serotonin (Hornby, 2001; Mittal et al., 2017). However, why nausea and vomiting symptoms are so common during pregnancy, and why they sometimes become so severe, remains to be elucidated.

HG symptoms may be limited to the first trimester (Gadsby et al., 1993; Verberg et al., 2005) or continue longer, in some cases even until the end of pregnancy (Bottomley et al., 2009; Louik et al., 2006). HG symptoms can occur at any time of day, or all day long, contrary to the concept of “morning sickness”, as mild NVP with symptoms possibly limited to the morning is sometimes called. For evaluating symptom severity, there are validated questionnaire tools such as the Pregnancy-Unique Quantification of Emesis (PUQE) score (Ebrahimi et al., 2009; Koren et al., 2002; Koren et al., 2005; Lacasse, Rey et al., 2008) and the Nausea and Vomiting in Pregnancy specific Quality of Life questionnaire (NVPQoL) (Koot et al., 2020; Lacasse et al., 2008). HG may cause complications, especially if the symptoms persist a long time. Possible complications of HG are presented in chapter 2.6.1, Effects of HG on the mother.

2.1.3 Treatment

HG patients often require hospital care. Commonly used criteria for hospitalization are persistent vomiting, weight loss of more than 5% of pre-pregnancy weight and ketonuria (The American College of Obstetricians and Gynecologists, 2018). Curative treatment for HG has not been discovered, and current treatment strategies aim at relieving symptoms and alleviating complications of HG, such as dehydration and malnutrition (American College of Obstetrics and Gynecology, 2018; Bottomley et al., 2009; McParlin, O'Donnell et al., 2016).

There are currently no official guidelines for treatment of HG in Finland, but hospitalization criteria and treatment protocols in clinical use have been described in

the Finnish medical journal Duodecim (Aitokallio-Tallberg et al., 2005; Laitinen et al., 2019).

Intravenous hydration is an important part of HG treatment, as oral intake of liquids is often difficult for the patient, and vomiting causes additional fluid loss. Dietary approaches such as trying which type of food could best be tolerated by the patient, may be attempted, but if oral food intake is too difficult for the patient, nutrients can be administered intravenously or by nasogastric tube feeding. (American College of Obstetrics and Gynecology, 2018; Grooten et al., 2017; Laitinen et al., 2019; Stokke et al., 2015). In HG treatment, it is important to take into account prevention of Wernicke's encephalopathy, an acute neuropsychiatric disorder caused by thiamine deficiency (American College of Obstetrics and Gynecology, 2018; Laitinen et al., 2019; Oudman et al., 2019).

Antiemetic medication recommendations for HG differ from country to country. In Finland, metoclopramide, a dopamine antagonist which improves gut motility, is the most commonly used pharmacologic treatment for HG. Ondansetron, chlorpromazine, meclizine and proton pump inhibitors, such as omeprazole, to alleviate heartburn, are also used in Finland. (Laitinen et al., 2019) In the United States, the first recommended pharmacologic HG treatment option is a combination of pyridoxine and doxylamine, followed by dimenhydrinate, diphenhydramine, prochlorperazine and promethazine, whereas metoclopramide, ondansetron, promethazine, trimethobenzamide, chlorpromazine and methylprednisolone are used for persistent HG symptoms (American College of Obstetrics and Gynecology, 2018). In the United Kingdom, first-line treatment options listed for HG are cyclizine, prochlorperazine, promethazine and chlorpromazine; second-line options are metoclopramide, domperidone and ondansetron, and corticosteroids are recommended as third-line treatment (Royal College of Obstetricians and Gynaecologists, 2016).

2.2 Incidence of HG

HG is a relatively rare condition. In nation-wide register-based studies, HG has been diagnosed in 0.3%–1.2% of pregnancies. In different hospital-based or medical record-based study settings, incidences up to 10.8% have been observed (**Table 4**).

The different incidences of HG in the five studies in the USA and the five studies in Norway emphasize that results regarding incidence of HG even within the same population are strongly affected by the data sources, as well as inclusion and exclusion criteria. When comparing incidences in different countries, results must be interpreted with caution, taking the study settings into consideration.

Table 4. Incidence of HG in different studies.

HG %	HG cases	Total N	Year(s)	Country	Data source	Reference
0.3%	3,068	989,073	1973–1981	Sweden	Swedish Medical Birth Register	Källén, 1987
0.3%	5	1,453	1988	Hong Kong	Caritas Medical Centre medical records	Chin, 1989
0.4%	137	35,093	2001–2010	France	Medical records of the Centre Hospitalier Régional Universitaire de Tours	Chraibi et al., 2015
0.5%	2,466	520,739	1999	United States	Patient discharge data and birth cohort data from the State of California	Bailit, 2005
0.7%	337	46,179	1997	United States	One national commercial managed care center (name undisclosed)	Gazmararian et al., 2002
0.7%	62	8,953	1986	Finland	The Northern Finland Birth Cohort	Koot et al., 2018
0.8%	1,301	157,922	1988–2002	Canada	Nova Scotia Atlee Perinatal Database	Fell et al., 2006
0.9%	8,296	900,074	1967–2005	Norway	Medical Birth Registry of Norway	Vikanes et al., 2008
0.9%	20,004	2,270,363	1967–2009	Norway	Medical Birth Registry of Norway	Vandraas et al., 2013
1.0%	7,938	781,725	1992–2001	Sweden	Swedish Medical Birth Register	Cedergren et al., 2008
1.0%	2,210	N/A (only percentage reported)	2013–2015	South Korea	Korea National Health Insurance claims database	Kim et al., 2020
1.1%	12,270	1,142,763	1997–2009	Sweden	Swedish Medical Birth Register	Bolin et al., 2013
1.1%	N/A (only percentage reported)	“Approximately 274,000 hospitalizations”	1991–1992	United States	National Hospital Discharge Survey	Bennett et al., 1998
1.1%	138	12,473	1984–1991	United States	Perinatal database of Hutzel Hospital/Wayne State University	Hallak et al., 1996

1.1%	398	37,442	1999–2008	Norway	The Norwegian Mother and Child Cohort Study	Owe et al., 2019
1.1%	353	33,467	1999–2008	Norway	The Norwegian Mother and Child Cohort Study	Vikanes et al., 2010
1.2%	814	71,468	1998–2008	Norway	The Norwegian Mother and Child Cohort Study	Vikanes et al., 2013
1.3%	184	13,630	2010–2013	Israel	Database of the Department of Obstetrics and Gynecology of Galilee Medical Center, Nahariya, Israel	Konikoff et al., 2016
1.5%	121,885	8,215,538	1997–2012	United Kingdom	The Hospital Episodes Statistics	Fiaschi et al., 2016
1.7%	753	45,333	1997–2009	Germany	A University hospital in Germany	David et al., 2012
2.1%* OR 9.1%	8,815 or 37,865	417,028	1998–2014	United Kingdom	Medical records (CPRD-GOLD)	Fiaschi et al., 2019
3.0%	N/A (only percentage reported)	3,295,970	1987–1992	United States	California Pregnancy Complication Surveillance System	Scott et al., 1997
3.6%	119	3,350	2002–2005	Japan	Kaizuka City Hospital medical records	Matsuo et al., 2007
4.5%	266	5,890	2000	Kuwait	Maternity Hospital Kuwait medical records	Al-Yatama et al., 2002
10.8%	201	1,867	1986–1987	China	Stratified random sample of 29 hospitals from Shanghai municipality	Zhang et al., 1991

*Depending on definition: 2.1% hospital admissions due to HG; 9.1% when combining hospital admissions, antiemetic treatment in primary care and recorded diagnoses.

2.2.1 Overall incidence of HG

HG affects approximately one in a hundred pregnancies. In Finland, this signifies approximately 600 HG pregnancies each year, and more than a million pregnancies worldwide. Across the world, both low, e.g. 0.3% in Hong Kong (Chin, 1989) and 0.4% in France (Chraibi et al., 2015) and high incidences of HG, e.g. 4.5% in Kuwait (Al-Yatama et al., 2002) and 10.8% in China (Zhang et al., 1991) have been reported.

In countries in which several studies have estimated the incidence of HG, the observed incidences vary somewhat. For instance, in the United States, incidences of HG ranging from to 0.5% (Bailit, 2005) to 3% (Scott et al., 1997) have been reported. These studies defined HG cases as women hospitalized due to HG, but as there are no comprehensive nation-wide registers regarding hospitalizations or medical follow-up of pregnancies in the United States, the data sources were variable: individual hospitals' databases (Gazmararian et al., 2002; Hallak et al., 1996), state-level patient discharge or pregnancy complication surveillance data (Bailit, 2005; Scott et al., 1997), or the National Hospital Discharge Survey (Bennett et al., 1998).

For some countries, only isolated studies regarding incidence of HG have been published, and for some countries, no data are available. The highest incidences have been reported outside of the most frequently studied regions, Europe and North America, but whether the different incidences are caused by actual biological differences between populations, or health care system-related differences, such as diagnostic criteria or reporting, cannot be determined.

2.2.2 Incidence of HG in the Nordic countries

In the Nordic countries, incidences of HG between 0.3% and 1.2% have been reported. In Norway and Sweden, several register studies have been carried out with quite uniform results, whereas less is known regarding HG in Denmark, Iceland and Finland.

In Norway, incidences between 0.9% and 1.2% have been reported (Owe et al., 2019; Vandraas et al., 2013; Vikanes et al., 2008; Vikanes et al., 2010; Vikanes et al., 2013). In two partly overlapping studies using data derived from the Norwegian Medical Birth Register covering 900,074 pregnancies in 1967–2005 (Vikanes et al., 2008) and 2,270,363 pregnancies in 1967–2009 (Vandraas et al., 2013), the incidence of HG was 0.9%. In the first study, only primiparous women were included, whereas the latter studied all singleton births. The other Norwegian studies used data from the Norwegian Mother and Child Cohort Study, with distinct study questions and thus partly differing inclusion and exclusion criteria. In one study, Vikanes et al. studied 33,467 primiparous deliveries in version IV of the cohort data set, while Owe et al. studied 37,442 primiparous deliveries in revised version VIII

of the data set, both studies covering years 1999–2008 and resulting in an incidence of HG of 1.1% (Owe et al., 2019; Vikanes et al., 2010). In another study, Vikanes et al. included 71,468 singleton deliveries covering years 1998–2008 and observed an incidence of HG of 1.2% (Vikanes et al., 2013). The lower incidences of HG in studies using the Norwegian Medical Birth Register compared to studies using the Norwegian Mother and Child Cohort Study may stem from the different time windows. In one of the Norwegian Medical Birth Register studies, the incidence of HG increased from 0.7% in 1967–1976 to 1.0% in 1997–2005 (Vikanes et al., 2008), and in another study, an incidence of HG of 1.4% was observed in a 1999–2009 sample of the data (Vandraas et al., 2013), suggesting that HG may not have been registered as frequently in the earlier years.

In studies using data derived from the Swedish Medical Birth Register, incidences between 0.3% and 1.1% have been reported (Bolin et al., 2013; Cedergren et al., 2008; Källén, 1987). One study covering years 1973–1981 observed an overall incidence of HG of 0.3% with results varying between different hospitals from 0% to over 1% (Källén, 1987). Another study covering years 1992–2001 found an incidence of HG of 1.0% (Cedergren et al., 2008), and in the most recent one, covering years 1997–2009, the incidence of HG was 1.1% (Bolin et al., 2013). The differences between hospitals observed by Källen et al., together with the low average incidence in their study, may indicate inconsistency in diagnostic practices in the 1970's, whereas the observed narrower ranges between the results of the two partly overlapping more recent studies suggest more commensurate diagnostic or reporting practices. The latter studies also combined data from the Hospital Discharge Register to the Birth Register, ensuring identification of HG cases.

In Denmark, one register study covering years 1980–1996 reported an incidence of HG of 0.8% (Basso et al., 2001). In another study combining data from Danish, Swedish and Norwegian birth registers, the incidence of HG in Denmark in 1977–2010 was reported to be 0.9%, but the numbers of HG cases nor the reference population were not reported separately regarding each country, and this result is thus not included in the incidence table (Vandraas et al., 2015).

Incidence of HG has not been studied in Iceland. In the Icelandic Study of Perinatal Mental Health conducted between 2006 and 2012, pregnancy complications of 503 women were assessed, (Jonsdottir et al., 2020) and 70 women (13,9%) reported vomiting during pregnancy. However, as vomiting was reported only in a yes/no scale and no information was available about its frequency or duration, nor eventual hospitalizations, no conclusion can be drawn regarding HG in Iceland, and these results are thus not included in the incidence table.

Earlier studies about the incidence of HG in Finland were sparse. In 1986, the proportion of women hospitalized due to HG in one cohort was 0.7%, but the number

of HG cases was only 42 women, and only inpatients were included (Koot et al., 2018).

2.3 Burden of illness caused by HG

Although relatively rare, HG causes a considerable burden of illness. HG has a major impact on the patients' general health, mental well-being, social life and daily activities such as household chores, care for children and capability to work, as well as an economic burden due to medical costs and loss of workdays (Attard et al., 2002; Havnen et al., 2019; Konikoff et al., 2016; Trovik et al., 2016). Women with HG need medical care to be able to maintain sufficient hydration and nutrition to carry out the pregnancy. Treatment can be organized in outpatient settings or by hospitalization.

Outpatient care of HG includes several treatment options such as dietary and lifestyle advice, antiemetic drugs, or intravenous fluid replacement (Fiaschi et al., 2019; Jueckstock et al., 2010; Kelly et al., 2011; McParlin et al., 2016). Compared to hospitalization, outpatient care is less costly (Murphy et al., 2016) and can be offered in varied settings, but systematic comparison of treatment outcomes in different settings is as yet sparse (Boelig et al., 2018). In one pilot randomized controlled trial, an outpatient regime of intravenous rehydration and active midwifery support was as efficient compared to routine inpatient care in terms of patient satisfaction and obstetric and neonatal outcomes (McParlin et al., 2016).

HG often requires inpatient care; HG is the most common reason for hospitalization in the first trimester of pregnancy in pregnancies resulting in delivery (Adams et al., 1994; Gazmararian et al., 2002). In hospital settings, patient monitoring, intravenous medication and ensuring adequate hydration and nutrient intake with parenteral nutrition or enteral tube feeding can be efficiently managed. Multiple admissions due to HG are not uncommon (Fiaschi et al., 2019; Godsey et al., 1991; Tan et al., 2009). Average length of hospitalization has been reported to be 2–5 days (Bailit, 2005; Derbent et al., 2011; Gazmararian et al., 2002; Konikoff et al., 2016; Koot et al., 2020; Tan et al., 2006).

On the population level, outpatient care is more common than inpatient care (Fiaschi et al., 2019), reflecting the symptom spectrum of HG with the most severe and persistent symptoms requiring hospitalization if outpatient management has failed (Clark et al., 2014). Timely and active outpatient care may also reduce the need of hospitalization (Kelly et al., 2011).

2.4 Recurrence of HG

Risk of having HG again in a following pregnancy is an important question for women having experienced HG (Dean et al., 2019; Koren et al., 2004). Although it is known that HG often recurs in following pregnancies, estimating the risk is not straightforward, as different studies have yielded widely varying results of recurrence rates ranging from 15% to 89% (Dean et al., 2019; Fejzo et al., 2011; Trogstad et al., 2005; Nijsten et al., 2021 a).

The observed recurrence rates appear to be strongly affected by the study methods: population-based register studies have yielded recurrence rates in the range of 15% to 26% (Fiaschi et al., 2016; Trogstad et al., 2005), whereas recurrence rates in survey-based studies have ranged from 71% to 89% (Fejzo et al., 2011; Fejzo et al., 2012; Magtira et al., 2015).

As HG occurs in approximately 1% of pregnancies in general, the increased likelihood of HG after an initial HG pregnancy is substantial and is to be considered when planning a new pregnancy. Treating symptoms of nausea and vomiting actively and without delay may prevent progression to HG, greatly improving the expecting mother's experience of pregnancy and quality of life (QoL) (Dean, 2014; Koren et al., 2004).

2.5 Etiology of HG

Several factors affecting the risk of HG have been proposed (Figure 2), and current consensus favours multifactorial etiology of HG (Fejzo et al., 2019; Verberg et al., 2005). Many maternal, environmental, or pregnancy-related factors may cause or aggravate HG, and individuals are likely to have distinct susceptibilities to different factors. Many of these factors may be linked to each other or share some common mechanisms of action, but as yet, not enough is known to establish a comprehensive picture of the pathophysiology of HG.

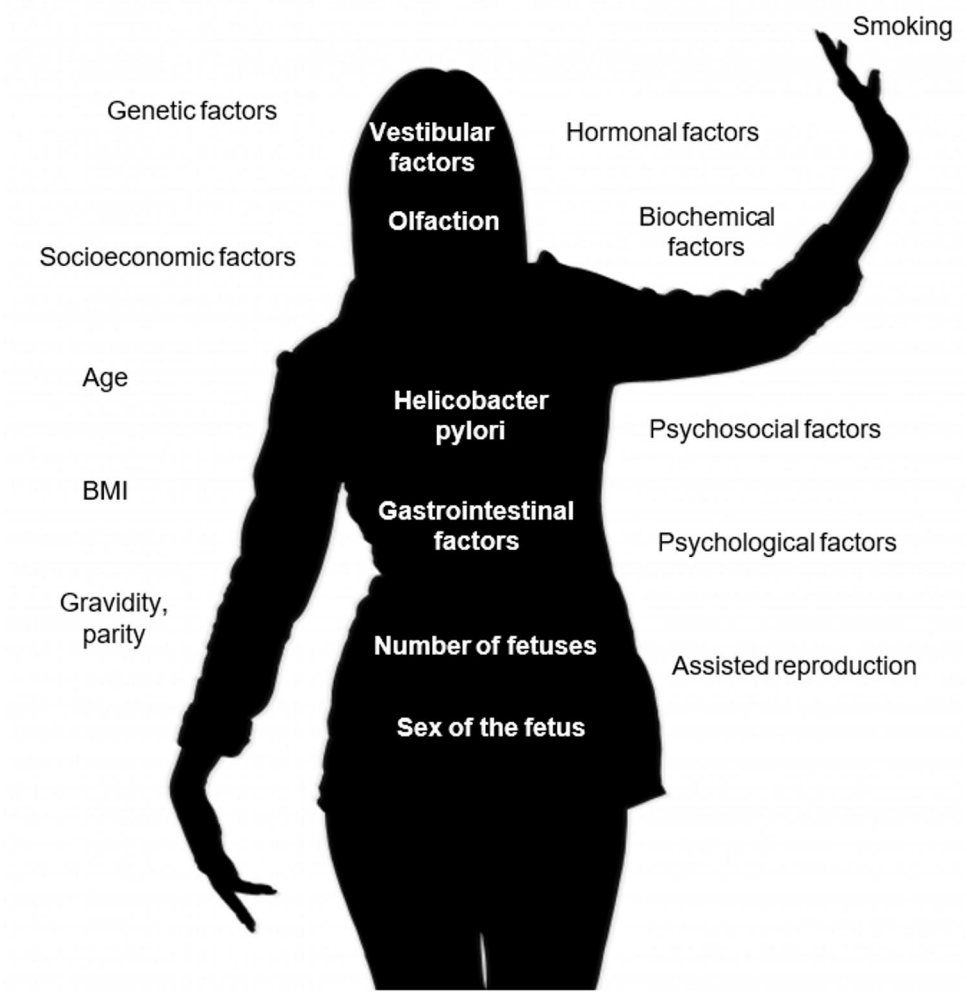

Figure 2. Factors affecting the risk of HG.

2.5.1 Maternal factors

Several maternal factors have been observed to be associated with HG. Some of the factors are likely to be connected to each other, and certain pathways of action have been proposed, but for the most part only correlations between HG and these factors have been discovered without detailed knowledge about the causal relations.

2.5.1.1 Hormonal and biochemical factors

Human chorionic gonadotropin (hCG), a glycoprotein hormone produced mainly by the placenta during pregnancy (Cole, 2010), has often been cited as having a central role in HG, based on the observation that maternal serum concentrations of hCG and symptoms of HG peak at approximately the same time in the first trimester of pregnancy (Figure 3) (Korevaar et al., 2015; Verberg et al., 2005).

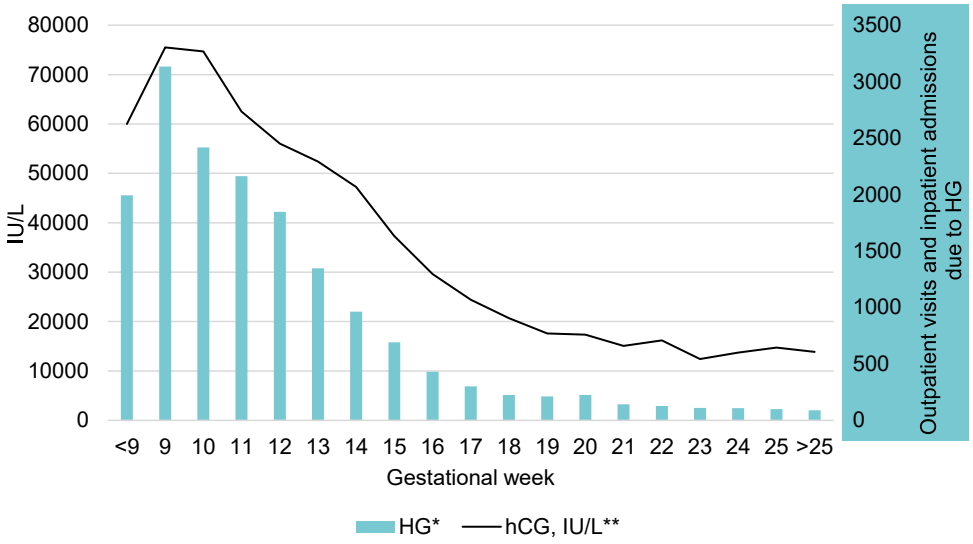

Figure 3. Timing of HG and maternal serum hCG concentrations by gestational weeks. *(author's data) **(Korevaar et al., 2015)

HG symptoms may arise in situations where maternal serum hCG levels are high, such as in multiple pregnancy (Bailit, 2005; Basso et al., 2001; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987; Morgan et al., 2017; Vikanes et al., 2008) or gestational trophoblastic disease (Hou et al., 2008; Lockwood et al., 2009; Mangili et al., 2014; Soto-Wright et al., 1995). Compared to pregnant women without HG, elevated serum concentrations of hCG have been observed in women with HG (Derbent et al., 2011; Hershman, 1999; Kauppila et al., 1979; Korevaar et al., 2015; Lee et al., 2003; Lockwood et al., 2009; Peled et al., 2012), and accordingly, hCG has been hypothesized to be one of the main causes of HG. In the brain, hCG is bound to the same receptor as luteinizing hormone (LH), LH/hCGR (also called hCG/LHR or LHCGR), initiating various physiologic effects (Cole, 2010; Lei et al., 2001). The LH/hCGR is also expressed in the gut (Hammar et al., 2012), indicating that a direct effect of hCG on the digestive tract is possible but its eventual role in

HG has not been examined. However, the hCG hypothesis does not pertain to all women: as hCG levels vary considerably between individual women (Korevaar et al., 2015; Peled et al., 2012), HG may occur without exceptionally elevated hCG, and some studies have reported no correlation between serum hCG concentration and HG (Dypvik et al., 2018; Panesar et al., 2001; Verberg et al., 2005). It thus appears that hCG may play a role in HG pathogenesis in certain individuals but is not alone sufficient to explain symptoms in all women.

Transient hyperthyroidism sometimes concurs with HG. In pregnancy-related hyperthyroidism, lower thyroid stimulating hormone (TSH) and higher serum T4 and T3 levels are observed (Arslan et al., 2003; Deruelle et al., 2002; Lockwood et al., 2009; Ndungu et al., 2009). However, these hormone levels at admission have not been found to predict severity or clinical course of HG (Nijsten et al., 2021 b). The increased thyroid activity and TSH suppression may be due to cross-reactivity between certain forms of hCG and TSH, resulting in a stimulating effect of hCG on the thyroid (Duman et al., 2015; Hershman, 1999; Sun et al., 2014). Transient hyperthyroidism is likely to be a separate side effect of this cross-reactivity rather than a contributor to HG symptoms, as demonstrated for instance by the observation that HG can occur after thyroidectomy, i.e. completely independently of thyroid activity (Blankenstein et al., 2009).

Serum estrogen levels rise significantly during pregnancy, and as some women may be susceptible to nausea in response to the elevated estrogen levels, estrogens have also been implied as a potential cause of symptoms of nausea and vomiting (Depue et al., 1987; Hudon Thibeault et al., 2019; Jarnfelt-Samsioe et al., 1986; Lagiou et al., 2003). However, results regarding estrogens in HG are inconclusive (Niemeijer et al., 2014; Verberg et al., 2005), and as estrogen secretion typically rises progressively towards the end of pregnancy, differing from timing of HG symptoms, it is not likely to play a major role in HG pathogenesis (Hudon Thibeault et al., 2019; Verberg et al., 2005). Estrogens have complex interactions with serotonin (Hudon Thibeault et al., 2019), and as serotonin is involved in signalling related to nausea and vomiting (Flake et al., 2004; Mittal et al., 2017), the observations associating estrogen and nausea may result from these interactions rather than as a direct individual effect of estrogens. Similarly to estrogen, both higher and lower progesterone levels have been reported in association with HG or nausea and vomiting (Niemeijer et al., 2014; Verberg et al., 2005), and its role in HG is unclear.

In one study analyzing maternal serum levels of some androgen hormones, lower concentrations of androstenedione and higher concentrations of androstanediol were observed among women with HG compared to healthy pregnant women, implicating altered steroid hormone homeostasis in at least some women with HG (Helseth et al., 2014).

Leptin and ghrelin, important in physiological processes regulating nutrition, have also been studied in association with HG. Both higher (Aka et al., 2006; Demir et al., 2006) and lower (Gungor et al., 2013) leptin levels have been observed in HG, and other studies have found no association between HG and leptin levels (Unsel et al., 2004). As leptin is involved in other processes occurring in HG, such as transient hyperthyroidism and energy metabolism disturbances, it may be that changes in leptin levels are not related to HG as such but rather a side effect related to other metabolic processes (Arslan et al., 2003). As for ghrelin, both increased (Albayrak et al., 2013; Oruc et al., 2013) and decreased (Ozturk et al., 2017) levels have been observed in HG, while in other studies, no differences have been found (Ege et al., 2019). Ghrelin stimulates appetite and promotes weight gain, and as HG strongly affects food intake, it has been hypothesized that the observed elevation of ghrelin levels in some HG patients is likely to be a reaction to the diminished energy intake rather than a causative factor in HG (Ege et al., 2019; Oruc et al., 2013). Others have hypothesized that in some women, the observed low ghrelin levels may contribute to lower appetite, thus further reducing the patients' energy intake (Ozturk et al., 2017).

Serotonin, or 5-hydroxytryptamine (5-HT) is a signalling molecule found prominently in the gut and the central nervous system (Banskota et al., 2019; Hudon Thibeault et al., 2019). In the gut, serotonin is involved in several processes, including fluid and mucus secretion as well as regulation of peristaltic movement (Banskota et al., 2019) and some pathways possibly leading to perception of nausea (Ohlsson et al., 2007). During pregnancy, serotonin is also secreted by placental trophoblast cells (Hudon Thibeault et al., 2019), and elevated plasma levels of serotonin have been observed in women with HG (Cengiz et al., 2015). Serotonin may also stimulate the medullary vomiting center in the brain, leading to nausea and vomiting (Flake et al., 2004; Mittal et al., 2017). Certain drugs used for treating HG, ondansetron, granisetron and dolasetron, target one of the several known serotonin receptors, 5-HT3 receptor (Flake et al., 2004; Tincello et al., 1996), and their effectiveness provides further assertion that serotonin metabolism probably plays a role in HG.

Dopamine, a neurotransmitter, may stimulate the medullary vomiting center in the brain (Flake et al., 2004). Dopamine antagonists such as metoclopramide, chlorpromazine and promethazine are effective against nausea and vomiting in some but not all women, indicating that in some cases, HG symptoms may be mediated by dopamine (American College of Obstetrics and Gynecology, 2018; Flake et al., 2004).

2.5.1.2 Genetic factors

Women with relatives affected with NVP or HG have been shown to be more likely to have NVP or HG in their pregnancies: interviews and surveys (Fejzo et al., 2008; Laitinen et al., 2020; Y. Zhang et al., 2010), cohort studies (Colodro-Conde et al., 2016) as well as population level studies (Vikanes et al., 2010) have documented this association. This points to a genetic element, and in the 2010s, first reports of which genes could be implied have emerged.

Certain alleles of growth differentiation factor 15 (GDF-15) (Fejzo et al., 2018; Fejzo et al., 2019), insulin-like growth factor binding protein 7 (IGFBP7) (Fejzo et al., 2018) and ryanodine receptor 2 (RYR2) (Fejzo et al., 2017) genes have been found to be more common among women with HG, but the roles of these genes in HG are not yet well known. GDF-15 is a regulatory protein important in placentation (Fejzo et al., 2018; Fejzo et al., 2019), and elevated serum levels of GDF-15 have been observed in cancer cachexia (Assadi et al., 2020) and in pregnant women with vomiting in second trimester of pregnancy, associated with symptom severity (Petry et al., 2018), suggesting that HG could in some cases be mediated by GDF-15. Insulin-like growth factor (IGF) is central in pregnancy, regulating for instance trophoblast invasion in the decidua (Derbent et al., 2011). Elevated levels of pregnancy-associated plasma protein A (PAPP-A), a protease targeting insulin-like growth factor binding proteins (Lawrence et al., 1999), have been observed in HG (Derbent et al., 2011), indicating a possible link between IGFBP7 and HG. Intracellular calcium release channel RYR2 is expressed in the vomiting center of the brain and could thus affect symptoms of nausea and vomiting (Fejzo et al., 2017).

However, genetic factors cannot explain all cases of HG, as the risk alleles of these genes are not found in all women with HG, whereas some women without HG also share these alleles: for instance, the G allele of the gene GDF15 is found among 80% of HG patients and 70% of symptom-free women, and the A allele of the gene IGFBP7 is found among 70% of HG patients and 65% of symptom-free women (Fejzo et al., 2018). Some women may experience HG in some but not all of their pregnancies (Dean et al., 2019), indicating that other circumstances in addition to genetic susceptibility are important.

2.5.1.3 Age

Younger age appears to be associated with increased risk of HG (Bailit, 2005; Fell et al., 2006; Fiaschi et al., 2016; Vikanes et al., 2013). The reason for this association is not known, but hormonal factors may play a role, as higher hCG levels during pregnancy have been measured in age groups below 25 years compared to ages between 25 and 35 years (Korevaar et al., 2015). However, as hCG levels follow a slightly U-shaped curve rising again in age groups over 35 years (Korevaar et al.,

2015), hCG levels alone cannot account for the increased risk of HG in younger maternal age.

2.5.1.4 Gravidity and parity

Gravidity, i.e. the number of pregnancies a woman has had, and parity, i.e. the number of deliveries she has had, have been extensively studied regarding HG. However, results about their association with HG are inconclusive: in some studies, HG has been found to be associated with primiparity (Fell et al., 2006; Fiaschi et al., 2016; Roseboom et al., 2011) and in others with higher gravidity or parity (Kjeldgaard, Eberhard-Gran, Benth, Nordeng et al., 2017; Vilming et al., 2001). Similarly, in studies assessing severity of HG, both lower (Godsey et al., 1991) and higher (Ellilä et al., 2018; Sharp et al., 2016) parity have been associated with more severe HG.

2.5.1.5 Body mass index

Body mass index (BMI) is commonly used for an approximate measure to determine if a person is underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) or obese (≥30 kg/m^2). HG appears to be more common among under- or overweight women compared to women in the normal weight range (Lindholm et al., 2015; Matsuo et al., 2007; Vikanes et al., 2010)

The effect of BMI on HG symptoms may be mediated by the effect of adiposity to hormonal activity during pregnancy: for instance, serum hCG levels correlate negatively with BMI, i.e. higher hCG levels have been measured among underweight than normal- or overweight pregnant women (Eskild et al., 2012; Korevaar et al., 2015), but exact mechanisms of action are not known.

2.5.1.6 Gastrointestinal factors

In addition to HG, other gastrointestinal symptoms are very common during pregnancy (Keller et al., 2008), and some of these factors may aggravate severity of HG symptoms (Gill et al., 2009; Walsh et al., 1996).

Gastric motility disturbances such as gastric slow wave dysrhythmias occur in gastrointestinal diseases and transient conditions such as motion sickness (Koch, 2002; Lien et al., 2003). In nausea and vomiting of pregnancy, both bradygastria and tachygastria, i.e. slower and faster than normal gastric waves have been observed (Jednak et al., 1999; Koch, 2002). In experimental settings, progesterone and estrogen have been shown to induce gastric dysrhythmias in healthy nonpregnant women (Walsh et al., 1996).

Acid reflux symptoms such as heartburn often co-occur with nausea and vomiting in pregnancy, and treatment of acid reflux with antacids or proton pump inhibitors has been shown to alleviate severity of NVP symptoms (Gill et al., 2009; Law et al., 2010). In addition to its antiemetic properties, metoclopramide may also relieve reflux symptoms by improving motility and gastric emptying (Body et al., 2016).

One study has proposed that a local effect of excess of sulphite, a nausea-inducing hydrogen sulphide (H2S) catabolite, could play a role in nausea and vomiting of pregnancy: increased H2S has been observed to be necessary for angiogenesis in the placenta and the fetus, and could lead to an increased sulphite concentration in the gastrointestinal tract, thereby causing symptoms of nausea and vomiting (Taylor, 2016). This hypothesis is in line with the observation that the thiol/disulphide balance differs between pregnant women with or without ketonuria (Ege et al., 2020), and the role of thiol/disulphide metabolism in HG warrants further studies.

Gut dysbiosis, i.e. increased proportion of potentially harmful bacteria or fungi and decreased amount of protective bifidobacteria have been observed in HG (Balci et al., 2020), indicating that abdominal flora may also play a role HG. However, it is not known whether treatment of gut dysbiosis with e.g. probiotics would be beneficial in HG, as it has not yet been clinically studied in women with HG. Knowledge about the topic will hopefully progress in the future; in ClinicalTrials.gov, one study about the effect of probiotics on gastrointestinal function during pregnancy has been registered (University of California Davis, 2020).

Helicobacter pylori, a gram-negative microaerophilic bacterium which can cause chronic gastritis, has been found in women with HG more commonly than in pregnant women without HG symptoms (Golberg et al., 2007; Mansour et al., 2009; Ng et al., 2018; Sandven et al., 2008; Sandven et al., 2009). H. pylori has been found in amniotic fluid as well, indicating that the infection may not be limited to the gastrointestinal tract (Aydın et al., 2020). H. pylori can be treated during pregnancy, and there are case reports of successful eradication of the bacterium alleviating or even completely curing HG symptoms (Strachan et al., 2000; Mansour et al., 2011). H. pylori colonization is very common worldwide. The reported prevalence varies considerably in different populations, from approximately one fourth of the population in Oceania and one third in Western Europe to nearly 80% in Central Asia and Africa (Hooi et al., 2017). In Finland, approximately half of the total population is affected (Hooi et al., 2017), but as the prevalence of H. pylori has consistently diminished over time and is highest among older generations, the contemporary prevalence among women in childbearing age can be estimated to be

lower than 20% (Sipponen, 1997). There are no studies about the association of H. pylori and HG in Finland.

2.5.1.7 Susceptibility to nausea or vomiting

Women susceptible to nausea and vomiting in situations other than pregnancy have been found to have a higher risk of nausea and vomiting (Laitinen et al., 2020). Women with migraine, a condition characterized by intense headaches often combined with symptoms of nausea and vomiting, have been observed to have HG more often than women without migraine, and women with HG have reported migraine headaches more often than women without HG, suggesting a common mechanism between these conditions (Heinrichs, 2002; Laitinen et al., 2020).

In motion sickness, the nausea and vomiting symptoms are mediated by a reaction of the vestibular system to movement, and differences in vestibuloocular function between HG patients and pregnant women without HG have been observed (Goodwin et al., 2008; Tulmaç et al., 2021). As some women with HG have had symptom relief with drugs such as antihistamines indicated for motion sickness (American College of Obstetrics and Gynecology, 2018; Flake et al., 2015), it is possible that in some women, HG pathogenesis may be mediated by the vestibular system.

2.5.1.8 Psychological factors

HG has been found to be associated with symptoms of depression and anxiety, measured with several validated questionnaires such as the Beck's Depression Inventory (Duman et al., 2015; Topalahmetoglu et al., 2017), the State Anxiety Inventory (Duman et al., 2015), the State-Trait Anxiety Inventory (McCarthy et al., 2011), the Perceived Stress Scale (McCarthy et al., 2011) or the Edinburgh Postnatal Depression Scale (McCarthy et al., 2011; Mitchell-Jones et al., 2020). An apparent association between HG and psychological disorders thus exists, but the cause/effect relation has been debated (Buckwalter et al., 2002; M. S. Fejzo, 2017; Mitchell-Jones et al., 2017; Mitchell-Jones et al., 2020; Munch, 2002). Some researchers have suggested that underlying psychological conditions or ambiguous feelings about their pregnancy could predispose women to HG (Cohen et al., 2007; Lub-Moss et al., 1997). However, others postulate the psychological distress to be evoked by HG symptoms rather than vice versa (Duman et al., 2015; Havnen et al., 2019; Meighan et al., 2005; Simpson et al., 2001). As the vast majority of HG patients have no psychological diagnoses prior to their HG pregnancy, whereas these symptoms arise during or after the pregnancy, psychological factors are unlikely to explain HG pathophysiology (Havnen et al., 2019; Meighan et al., 2005). Psychological

symptoms related to HG during pregnancy are often transient and alleviate when the nausea and vomiting subside (McCarthy et al., 2011; Simpson et al., 2001), and current consensus tends to consider psychological symptoms to be a reaction to the burden of intractable nausea and vomiting.

2.5.1.9 Other maternal factors

Other possible etiologies of HG related to e.g. olfaction, immune system, and vitamin deficiencies have been proposed, but data about them are sparse.

Pregnant women often experience a sharpened sense of smell (Cameron, 2014). Sometimes the enhanced sense of smell becomes disturbing, if unpleasant odours are perceived too strongly, or if previously pleasant or neutral odours such as food preparation, become disagreeable (Swallow et al., 2005). It has been hypothesized that if there is an association between olfaction and HG, it may be mediated by a common mechanism with migraine headaches, also aggravated by some smells (Heinrichs, 2002).

In pregnancy, the maternal immune system undergoes adaptations permitting the mother's body to safely host the fetus (Fuhler, 2020; Minagawa et al., 1999), and it has been suggested that these changes, or their aberrant action, could cause HG (Minagawa et al., 1999; Verberg et al., 2005). However, no clear immunologic patterns relating to HG have been found. Some signs of an overactive immune system in women with HG have been observed, such as elevated neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (Kan et al., 2020), as well as higher levels of interleukin 6 or C-reactive protein (Engin-Ustun et al., 2013; Kan et al., 2020), but in other studies, no differences in these markers have been found (Tunc et al., 2016; Yilmaz et al., 2016).

The role of vitamin status or deficiencies in HG is not well known. Taking vitamins before conception and in early pregnancy has been associated with lower odds of NVP (Källén et al., 2003). Vitamin B6 supplementation can in some women relieve nausea and vomiting (Ensiyeh et al., 2009; Sharifzadeh et al., 2018). In one study, decreased total antioxidant status and increased nitric oxide levels were observed in women with HG (Beyazit et al., 2018), suggesting that the subject merits further research.

In one study, women who participated in leisure-time physical activity less than once a week before pregnancy had higher odds of HG both in unadjusted comparison and when adjusted for BMI and smoking (Owe et al., 2019). It could thus be hypothesized that pre-pregnancy physical activity could be a possible option for diminishing the risk of HG, emphasizing that these results only pertain to pre-pregnancy physical activity, as maintaining activity while suffering from severe HG is not feasible and should not be proposed as a remedy. Also, it is not known whether

other factors, physical conditions or health concerns may affect both the risk of HG and the ability to participate in leisure-time physical activity, indicating that these results should be interpreted with caution.

2.5.2 Environmental factors

As discussed earlier, HG does not always recur in pregnancies following a hyperemetic pregnancy, with reported recurrence rates of 15–89% depending on the study settings (Dean et al., 2019; Fejzo et al., 2011; Trogstad et al., 2005; Nijsten et al., 2021 a), and changes in circumstances from one pregnancy to another are likely to have an effect on symptoms of nausea and vomiting.

2.5.2.1 Smoking

Smoking has consistently been found to be associated with a moderately decreased risk of HG (Bolin et al., 2013; Fell et al., 2006; Vikanes et al., 2010). In population-scale HG studies where smoking status during pregnancy has been covered, 0.9%–1.2% of non-smoking women and 0.6%–0.8% of women who reported smoking during pregnancy have been observed to suffer from HG (Fell et al., 2006; Vikanes et al., 2010). The mechanism of the effect of smoking on nausea and vomiting is not known, but one hypothesis is the detrimental effect of tobacco on the placenta. In pregnancies with HG, higher placental weight has been observed (Vandraas et al., 2013), whereas smoking during pregnancy has been shown to reduce placental weight (Larsen et al., 2018), possibly by causing apoptosis of hCG-producing syncytiotrophoblast cells in the placenta (Vogt Isaksen, 2004). Smoking has also been associated with decreased blood flow in the placenta (Pintican et al., 2019), lower blood serum hCG concentrations (Korevaar et al., 2015) and adverse fetal effects (Jaakkola et al., 2004).

Studies regarding the effect of exposure to secondhand smoke, e.g. by partner's smoking, on HG are less numerous. In one study, non-smoking pregnant women with a smoking partner had a slightly increased risk of HG in unadjusted analysis, but not in adjusted analysis taking into account other maternal factors such as age and BMI (Vikanes et al., 2010). In another study, paternal smoking was associated with increased risk of severe vomiting (Zhang et al., 1991), and in one study focusing on the effect of environmental tobacco smoke on miscarriage, pregnant women exposed to secondhand smoke had symptoms of nausea and vomiting more frequently than unexposed women and women who themselves smoked (George et al., 2006). The reason for the discordance between the effect of smoking and exposure to secondhand smoke on HG is not known, but as being exposed to secondhand smoke may be less regular, e.g. in work-related tobacco exposure, it may

not have a strong enough effect on the placenta to reduce HG symptoms. Pregnant women have reported finding cigarette smoke more disagreeable than non-pregnant women, and being exposed to secondhand smoke may thus aggravate nausea in some women in the same way as other offensive smells (Cameron, 2014).

2.5.2.2 Psychosocial factors

Women in psychosocially vulnerable situations, such as living alone or lack of social support, have been observed to be more likely to have nausea and vomiting in pregnancy or to be hospitalized due to HG (Bailit, 2005; Chou et al., 2003; Farbu et al., 2014; Kramer et al., 2013; Markl et al., 2008).

Marital or cohabiting status may reflect the availability of support in daily life and can be associated with other unfavourable lifestyle factors. In one study, single mothers not only were at higher risk of nausea and vomiting but also had lower dietary quality during pregnancy, smoked more and were more likely to experience depression compared to married and cohabiting women (Farbu et al., 2014). In another study, women with HG were less likely to be married compared to women without HG (Bailit, 2005). The majority of pregnant women live with their spouse, and living alone may either be a choice or result of an unexpected event such as death of spouse or separation during the pregnancy, thus causing distress not directly related to the pregnancy but likely to affect the expecting mother. However, living with a partner does not necessarily assure adequate support, as the majority of women suffering from nausea and vomiting have also reported being affected by lack of support by their spouse (Mazzotta et al., 2000). Also, HG has not uniformly been found to be associated with living alone: in one study, there was no difference in marital status between women with HG, NVP or no symptoms (D'Orazio et al., 2011), and in another study, HG was less prevalent among single than married women (Vikanes et al., 2008).

Immigrant women have been more likely to be hospitalized due to HG than native women in several countries, e.g. Germany (David et al., 2012), the United Kingdom (Fiaschi et al., 2019) and Norway (Vikanes et al., 2008). When interviewed, immigrant women have brought up the negative impact of living out of their familiar environment and without their extended family, thus missing important sources of support during pregnancy (D. Groleau et al., 2019; D. Groleau, 2005).

2.5.2.3 Socioeconomic factors

The association between symptoms of HG or nausea and vomiting in pregnancy and socioeconomic status has been assessed using different variables for measuring socioeconomic status: employment status (Kramer et al., 2013; Källén et al., 2003;

Markl et al., 2008), education (D'Orazio et al., 2011; Munch et al., 2011; Weigel et al., 2000), or average price of housing in home address (Roseboom et al., 2011), and the results have indicated lower socioeconomic status to be associated with higher risk.

As relations between socioeconomic factors, individual life circumstances, symptoms of HG and quality of life are complex, causal relations between these situations cannot be easily deduced (Munch et al., 2011). In some situations, women in better socioeconomic status may have easier access to health care services, which could influence their symptoms of nausea and vomiting, but as socioeconomic differences have been found to be associated with poor outcomes also in countries where prenatal care is equally available to the whole population, the question remains uncertain. Low socioeconomic status can also mediate the risk of HG by increasing prevalence of other known risk factors for HG, such as H. pylori infection (Karaca et al., 2004).

2.5.3 Pregnancy-related factors

As environmental factors, individual pregnancy characteristics such as the method of conception, fetal sex and number of fetuses, have been shown to affect the risk of HG.

2.5.3.1 Assisted reproductive technology

In pregnancies conceived by ART, a higher risk of HG has been observed (Roseboom et al., 2011). Reasons for the increased risk are not known, but hormonal factors related to either the ART process, or underlying factors affecting both the mother's fertility and her risk of HG, may play a role.

Different ARTs may have different effects, as some of the techniques include treatments that cause more changes in hormonal levels. For instance, conception by ovulation induction has been associated with lower risk of HG compared to in vitro fertilization (Bordi et al., 2017). Nausea is a typical symptom in ovarian hyperstimulation syndrome (OHSS), a potentially lethal condition occurring as a side effect of ovarian stimulation (Humaidan et al., 2016). In one case series, ovarian stimulation caused HG-like OHSS symptoms in three women with history of HG who underwent IVF for ovum donation to have biological offspring by means of gestational surrogacy to avoid a new HG pregnancy (Fejzo et al., 2010). Even without pregnancy, the women with history of HG experienced severe nausea and vomiting during the ovarian stimulation treatment, indicating that women with HG may be especially prone to OHSS.

2.5.3.2 Number of fetuses

Many studies have established an association between multiple pregnancy and HG: multiple fetuses are more common in HG than in non-HG pregnancies (Bailit, 2005; Basso et al., 2001; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987; Morgan et al., 2017; Vikanes et al., 2008).

The mechanism behind this phenomenon is not known, but as higher maternal serum concentrations of hCG have been observed in multiple pregnancies, it has been proposed that hCG may be at least one mediating factor between the number of fetuses and HG (Eskild et al., 2012; Morgan et al., 2017; Verberg et al., 2005).

2.5.3.3 Sex of the fetus

In every country worldwide, more boys are born than girls: in the absence of gender discrimination or interference, the expected sex ratio at birth is estimated by WHO to be around 105 boys per 100 girls (World Health Organization, 2020 b). However, in HG pregnancies, the sex ratio has been found to be inversed: in HG pregnancies, female fetuses are more common than male, with sex ratios ranging from 80 to 94 boys per 100 girls (Basso et al., 2001; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987; Peled et al., 2013; Roseboom et al., 2011) (**Figure 4**). The reason for this is not known, and hypotheses proposed as to the possible mechanism mention hormonal factors such as higher maternal serum hCG (Deruelle et al., 2002; Korevaar et al., 2015; Peled et al., 2013) or estrogen (Fiaschi et al., 2016) associated with female fetus.

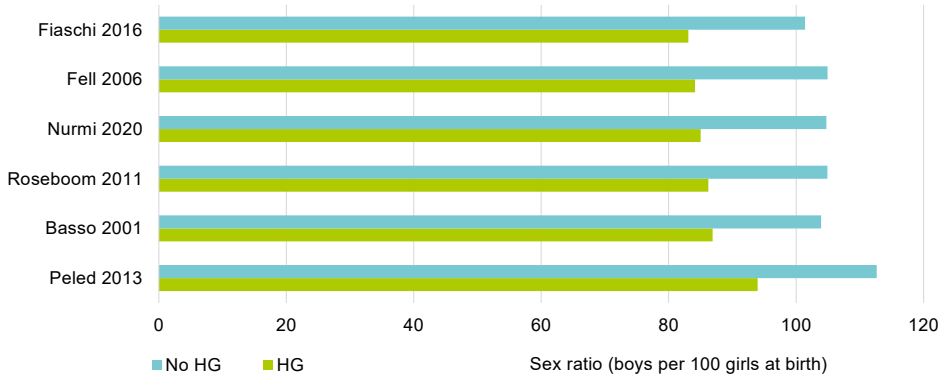

Figure 4. Sex ratios in pregnancies with HG and pregnancies without HG.

Even though most studies address the question from the point of view that the female fetus may have an effect on HG, data regarding the timing of altered hormonal levels

associated with female fetus are sparse, and it has also been proposed that the association could be inverse or accounted for by hormone levels at time of conception causing both HG symptoms and selection bias favoring female offspring, thus resulting in the observed higher number of female births in HG pregnancies (James, 2008; James, 2012).

2.6 Effects of HG

HG may have temporary or long-term effects on the pregnancy, the mother and the child. The complications can to some extent be alleviated with adequate care (American College of Obstetrics and Gynecology, 2018). Even when effective treatment cannot be found in every case, the disposition of medical personnel is important for women with HG; when interviewed, HG patients have expressed frustration and fear of not being taken seriously, and such feelings may affect their prospects of future pregnancies and trust in medical care in general (Havnen et al., 2019).

2.6.1 Effects of HG on the mother

HG causes severe discomfort and may induce vomiting-related side effects such as esophageal irritation, esophageal rupture, Mallory–Weiss syndrome, hematemesis, (Fejzo et al., 2009; Goodwin, 2008), retinal hemorrhage, retinal detachment, valsalva retinopathy (Ramskold et al., 2012), rupture of capillaries in facial skin causing bruising around the eyes (Bhanja et al., 2021), diaphragmatic tear (Chen et al., 2012), pneumomediastinum (Foley et al., 2020; Goodwin, 2008; Scarborough et al., 2020), and dental erosion due to repeated exposure to gastric acid and difficulties in brushing the teeth efficiently due to an exacerbated gagging reflex (Steinberg et al., 2013). Complications caused by prolonged bedrest, such as venous thromboembolism, may also occur (Fiaschi et al., 2018). When vomiting and inability to eat or drink persist, metabolic issues such as electrolyte imbalance arise (London et al., 2017; Summers, 2012), as well as vitamin deficiencies, such as vitamin K deficiency leading to insufficient blood coagulation (Baba et al., 2016; Devignes et al., 2009). Prolonged starvation and electrolyte imbalance may result in cardiac symptoms (Mitchell et al., 2017; Walch et al., 2018) or severe metabolic acidosis (A. Patel et al., 2011). Inability to cope with daily tasks and socioeconomic effects such as lost days of paid work are frequent in HG (Piwko et al., 2013).

Weight loss is one of the most common effects of HG, and it has also been included in most definitions of HG and indications of hospital treatment for HG (Erick, 2014; Goodwin, 2008; Grooten et al., 2015; Jansen et al., 2020). The weight loss can be caused not only by vomiting but also by the inability of oral intake of

nutrition; some women suffer from extreme nausea prohibiting them from eating or drinking almost at all (Erick, 2014; Ogawa et al., 2017).

HG may also cause changes in the liver, such as liver enzyme elevation, sometimes severe but without permanent hepatic damage (Bacq, 2011; Derbent et al., 2011; Gaba et al., 2020; Kamimura et al., 2015). In most cases, the liver enzyme elevation is transient: when HG symptoms resolve, liver function returns to normal (Bacq, 2011; Conchillo et al., 2002). In some studies, an increased risk of pre-eclampsia, a condition occurring in 5%–10% of pregnancies in the third trimester and characterized by hypertension, proteinuria and edema (Leeman et al., 2016) has been found among women hospitalized due to HG (Bolin et al., 2013; Fiaschi et al., 2018). However, the mechanisms of action and pathways between these conditions are not well known, and in other studies, this association has not been found (Koudijs et al., 2016).

Transient hyperthyroidism often concurs with HG, possibly because of the structural similarity between hCG and TSH, resulting in marked thyroid stimulation by hCG (Duman et al., 2015; Fiaschi et al., 2016; Goodwin et al., 1992; Sun et al., 2014). Hyperthyroid symptoms usually occur in the beginning of pregnancy when maternal serum hCG levels are highest and alleviate towards the end of pregnancy without causing permanent effects.

HG may also be associated with long-term symptoms such as postnatal depression (Meltzer-Brody et al., 2017; Poursharif et al., 2008) or post-traumatic stress disorder (Christodoulou-Smith et al., 2011) and even thoughts of suicide (Nana et al., 2021). In one study, women with HG reported emotional distress six months postpartum more often than women without HG, but in follow-up 18 months postpartum, the effect had dissipated (Kjeldgaard, Eberhard-Gran, Benth, & Vikanes, 2017), whereas in another study, the symptoms persisted after two years postpartum (Kjeldgaard et al., 2019).

Long-term effects of HG on other medical conditions are not well known. HG has been found to be inversely associated with overall maternal cancer risk and some cancer types such as cancer in the lungs, cervix or rectum (Vandraas et al., 2015), whereas other, such as thyroid cancer (Vandraas et al., 2015) and HER2-enriched breast tumours (Wright et al., 2018) have been observed to be more common among women with HG, and others, e.g. overall breast cancer risk, have not shown association with HG (Erlandsson et al., 2002; Wright et al., 2018).

Treatment of HG may in some cases cause complications, as well. Even though drugs approved for treatment of HG are generally safe for both the mother and the fetus, adverse drug reactions may occur, such as extrapyramidal symptoms associated with metoclopramide (Mishriky et al., 2012; Tianyi et al., 2017), and prolonged QT interval in ECG as a side effect of ondansetron (Moffett et al., 2016; J. Patel, 2013). Prolonged intravenous treatment may cause complications such as

central line associated bloodstream infections (Cape et al., 2014; Holmgren et al., 2008; Katz et al., 2000; Stokke et al., 2015). Refeeding syndrome, a potentially perilous condition caused by reintroduction of glucose after prolonged malnutrition, must be taken into consideration. It involves a cascade of reactions resulting in acute electrolyte imbalance, which in turn may cause arrhythmias, anemia, ischemia, muscle dysfunction, rhabdomyolysis, and multiple organ failure (Boateng et al., 2010; Mayer et al., 2019). To prevent refeeding syndrome, slow and gradual reintroduction of nutrition after starvation is recommendable, along with adequate electrolyte and vitamin supplementation and careful monitoring of electrolyte levels, fluid balance and ECG (Mayer et al., 2019).

2.6.2 Effects of HG on the offspring

Despite the substantial burden of HG on the mother, only few effects of HG on the fetus and baby have been observed. Ordinary symptoms of nausea and vomiting have been associated with generally good pregnancy outcomes (Czeizel et al., 2004; Furneaux et al., 2001; Koren et al., 2014; Maconochie et al., 2007; Nulman et al., 2009), but as HG symptoms are considerably more severe than common NVP, these conclusions cannot be directly applied to HG. For instance, favorable neurodevelopmental effect of NVP on offspring has been observed (Nulman et al., 2009), but in one study regarding HG, attention disorders, learning delay, sensory disorders, and speech and language delay were more common in children exposed to HG in utero compared to children of unaffected mothers (Fejzo et al., 2015). In a study comparing different degrees of NVP, emotional and behavioural problems such as symptoms of depression and anxiety were more common among children exposed to severe NVP (Syn et al., 2021). Poor pregnancy outcomes may result among HG patients with prolonged malnutrition, vitamin deficiencies and weight loss (Goodwin, 2008; Kawamura et al., 2008; Meinich et al., 2020).

HG has been associated with lower risk of miscarriage (Bashiri et al., 1995; Morgan et al., 2017) and stillbirth (Fiaschi et al., 2018), but in other studies, no association has been found (Bolin et al., 2013; Hallak et al., 1996; Koudijs et al., 2016; Kuru et al., 2012; Vandraas et al., 2013). Data regarding the effect of HG on preterm birth are inconclusive: increased likelihood of preterm birth has been observed in some studies (Dodds et al., 2006; Duman et al., 2015; Fejzo et al., 2013; Fiaschi et al., 2018), but not in others (Agmon et al., 2019; Fejzo et al., 2009; Grooten et al., 2015; Hastoy et al., 2015; Kleine et al., 2017; Kuru et al., 2012; Stokke et al., 2015; Tan et al., 2007; Vandraas et al., 2013).

One often reported effect of HG on the newborn is lower birth weight compared to those not exposed to HG (Fiaschi et al., 2018; Koudijs et al., 2016; Källén, 1987), although in other studies, no difference has been found (Duman et al., 2015; Fejzo

et al., 2013; Kuru et al., 2012; Tan et al., 2007). In several studies, an association between HG and the newborn's risk to be small for gestational age at birth has been observed (Bailit, 2005; Bolin et al., 2013; Dodds et al., 2006; Fiaschi et al., 2018; Meinich et al., 2020; Vlachodimitropoulou-Koumoutsea et al., 2013), but this association has not been confirmed in all populations (Agmon et al., 2019; Koudijs et al., 2016; Kuru et al., 2012; Stokke et al., 2015; Vandraas et al., 2013; Vikanes et al., 2013). Among HG patients, those who have lost more than 5% of their pre-pregnancy weight during pregnancy have had smaller babies than HG patients who have not lost as much weight (Gross et al., 1989). Thus, the effects of HG on fetal growth may result from prolonged malnutrition and become observable mainly in cases of intractable symptoms when sufficient nutrition cannot be ensured.

Nausea and vomiting have been associated with lower risk of congenital malformations (Anderka et al., 2012; Boneva et al., 1999; Czeizel et al., 2006), but studies regarding HG are sparser: in one study, the risk of congenital malformations in HG pregnancies has been reported to be lower (Czeizel et al., 2003) but in another, no difference was observed (Bashiri et al., 1995). In one study, babies of women with severe nausea and vomiting in early pregnancy had higher likelihood of neural tube defects (Lu et al., 2015), but when the study population was stratified according to use of folic acid supplementation, the effect was only seen among women who did not take folic acid, and the defects could have been caused by insufficient folate status, a known risk factor of neural tube defects (Greene et al., 2014). As several vitamin and other nutrient deficiencies have been associated with adverse pregnancy outcomes (Hovdenak et al., 2012; Koren et al., 2018), these findings emphasize the importance of nutritional supplementation, as HG may reduce the mother's ability to take in sufficient amounts of essential nutrients from food.

Low birthweight and other effects of HG related to malnutrition may carry long-term effects as seen in children of mothers suffering from starvation during pregnancy (Roseboom et al., 2000) In one study, reduced insulin sensitivity in childhood was observed in children whose mothers had severe HG (Ayyavoo et al., 2013), indicating a persistent effect on metabolism. However, in another study, no difference in BMI, blood pressure, fasting glucose or lipid levels between adolescents born to mothers with and without HG (Koot et al., 2017). To elucidate long-term effects of HG exposure in utero, further research is needed.

2.6.3 Effects of HG on family planning

In interviews and surveys, women who have experienced HG have expressed considering not to become pregnant again due to HG (Fejzo et al., 2011; Heitmann et al., 2017), considering pregnancy termination or having terminated a pregnancy due to HG (Havnen et al., 2019; Mazzotta et al., 2000; Meighan et al., 2005; Nana

et al., 2021; Poursharif et al., 2007; Nijsten et al., 2021 a). The effect of HG on the total number of children a woman will have in her lifetime has not been studied, but it could be expected that women's decision not to have more children due to HG may lead to them having fewer children compared to women without HG.

Female sterilization is a permanent method of contraception, chosen by women who have completed their childbearing (American College of Obstetrics and Gynecology, 2019), and as women with HG have expressed their intention not to have further pregnancies due to HG (Fejzo et al., 2011; Heitmann et al., 2017), sterilization could be their choice. However, research about the subject is sparse. There are several methods of female sterilization techniques, including tubal occlusion by electrocoagulation or mechanical devices, or tubal excision. In Finland, approximately 800–1800 sterilizations/year were performed in 2005–2017 (**Figure 5**).

In addition to HG, every woman has their own individual life situation with several other aspects to consider when deciding whether or not to have more children. Circumstances also tend to change over time, possibly leading women to revise and change their earlier plans or decisions.

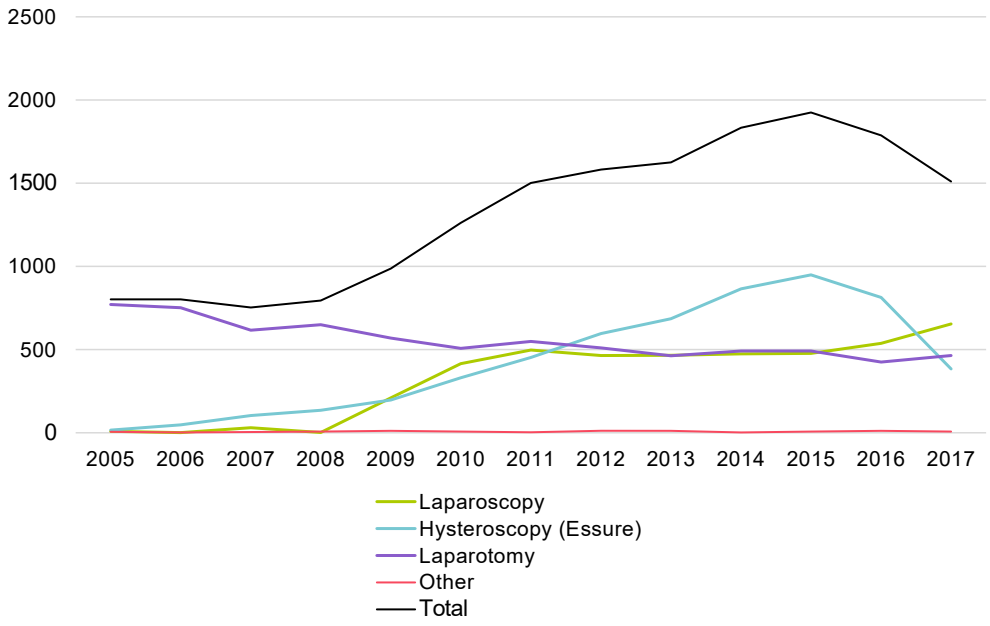

Figure 5. Frequencies of female sterilization procedures in Finland, 2005–2017.

3 Aims

The present study aimed at measuring the incidence and recurrence rate of HG in Finland, as well as the need of hospital and outpatient treatment due to HG, including assessment of associations between various maternal, environmental, and pregnancy-related factors in each of these settings. In addition, association of HG with family planning was evaluated.

Specific aims:

1. To evaluate the incidence of HG in Finland, and to assess maternal, environmental, and pregnancy-related factors in association with HG. **(Study I)**
2. To measure outpatient care and hospitalizations of HG in Finland, and to assess maternal, environmental, and pregnancy-related factors in association with readmissions due to HG during the same pregnancy. **(Study II)**
3. To estimate the recurrence rate of HG in Finland, and to assess maternal, environmental, and pregnancy-related factors in association with HG recurring in following pregnancies. **(Study III)**
4. To evaluate the effect of HG on family planning: deliveries, pregnancy terminations and sterilizations. **(Study IV)**

4 Materials and Methods

4.1 Registers

Finnish health care registers are a valuable and reliable source of information related to health care (Gissler et al., 2010; Sund, 2012). Registers are suitable for population-scale research of many topics tedious or impracticable to study with other methods.

The registers used in the present study are maintained and controlled by the Finnish Institute for Health and Welfare. Register data are collected for statistics, health care planning, and research purposes. The data contents are confidential, but the Institute for Health and Welfare may grant permission to use data for scientific research (**Figure 6**).

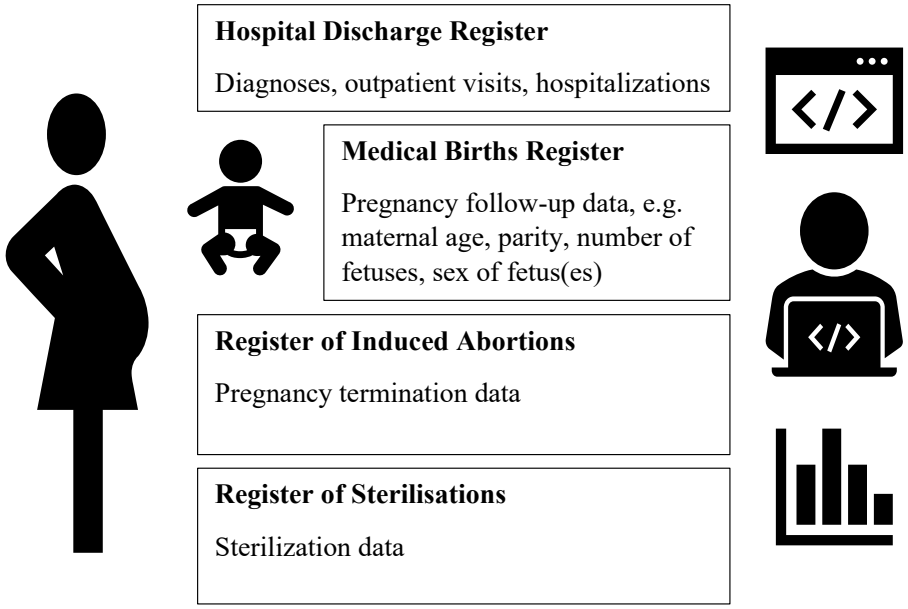

Figure 6. Registers for medical diagnoses, pregnancies, births, pregnancy terminations and sterilizations in Finland.

4.1.1 Finnish Hospital Discharge Register

Officially named Care Register for Health Care, the register contains data of specialised outpatient care patients and inpatients in Finland (Finnish Institute for Health and Welfare, 2020a). The Finnish Hospital Discharge Register (FHDR) was founded in 1969 and was renamed the Care Register for Health Care in 1994 to reflect the wider data content compared to the original setup. However, as similar registers in other countries are as a rule called hospital discharge registers, the former name is used in scientific correspondence in consideration of the international readership. In the original publications of Studies I–IV, as well as in this thesis, the register is called the FHDR.

The purpose of the register is to collect data on clients of hospitals. The register covers all inpatient care since 1969 and public hospital outpatient care since 1998. In practice, data are entered in the register annually as care notifications, following instructions provided by the Finnish Institute for Health and Welfare. Discharge diagnoses are given according to diagnostic criteria by physicians treating the patients. At the time of data collection for the present study, the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was in effect.

4.1.2 Finnish Medical Birth Register

The Finnish Medical Birth Register (FMBR) contains data about live births and stillbirths of babies weighing at least 500 g or born at the earliest on gestational week 22+0, as well as maternal data collected during pregnancy and at the time of delivery (Finnish Institute for Health and Welfare, 2020b). The FMBR was founded in 1987 and has been revised in 1990, 1996, 2004 and 2017.

The purpose of the register is to collect data for developing and organising maternity care, obstetrical services, and neonatal care. Data content of the FMBR covers maternal data at the beginning of pregnancy, monitoring and follow-up during pregnancy, including pregnancy- and delivery-related ICD diagnoses, details of the delivery and data regarding the infant until the age of 7 days or discharge.

4.1.3 Finnish Register of Induced Abortions

Registering pregnancy terminations is statutory in Finland, and data regarding them are collected in the Register of Induced Abortions controlled by the Finnish Institute for Health and Welfare (Finnish Institute for Health and Welfare, 2020c). The numbers of induced abortions have been collected since 1950, and the data contents of the register have been expanded in several revisions.

The register contains information on all legal pregnancy terminations in Finland. Cases are reported by the physician performing the termination within one month of the procedure using a specific data collection form approved by the Ministry of Social Affairs and Health. The register contains personal identity code of the woman and details regarding the pregnancy termination, including legally determined grounds for the termination. According to Finnish legislation, a pregnancy can be terminated if 1) the woman's life or health is at risk; 2) if pregnancy or delivery were a considerable burden to the woman; 3) the pregnancy resulted from rape, incest or other reasons stated in Finnish penal law; 4) the woman was younger than 17 or older than 40 years at time of conception, or if she had given birth to four or more children; 5) the fetus is suspected or confirmed to have an anomaly or severe illness; or if 6) the mother or the father is not capable to take care of the child (Finlex, 1970a). In practice, the law is interpreted liberally, and social reasons are the most common justification for termination of pregnancy (Heino et al., 2018). Pregnancy termination is to be performed as early as possible, and the permission procedures depend on gestational age and the mother's situation. In pregnancy with gestational weeks ≤ 12+0, authorisation by one clinician is required when the mother is younger than 17 years or older than 40 or if she has given birth to four or more children; in other cases, authorisation by two clinicians is required. Between gestational weeks 12+1 and 20+0, permission by the National Supervisory Authority for Welfare and Health (Valvira) is required. In cases of fetal anomaly or severe illness, the upper limit is gestational week 24+0.

4.1.4 Finnish Register of Sterilisations

As pregnancy termination data, registering sterilisations is statutory in Finland, and data regarding them are collected in the Register of Sterilisations controlled by the Finnish Institute for Health and Welfare (Finnish Institute for Health and Welfare, 2020d). The first Act on Sterilisation was decreed in 1935, initiating collection of sterilisation statistics.

All sterilizations performed in Finland are entered in the register, reported by physicians performing the procedure using a specific data collection form approved by the Ministry of Social Affairs and Health. The register contains the personal identity code of the woman and details regarding the procedure, including legally determined grounds for the sterilisation. According to Finnish legislation, a person may upon her request be sterilized, if 1) she has given birth to three children or has three underage children together with her spouse; 2) she is older than 30 years; 3) pregnancy would endanger her life or health; 4) other forms of contraception are unfeasible; 5) there is reason to expect that her offspring are likely to have an

anomaly or severe illness; 6) she is not capable to take care of children; or if 7) the person is transgender (Finlex, 1970b).

4.2 Definitions and procedures

HG pregnancies were defined by the presence of an HG diagnosis in the FHDR (ICD-10 diagnosis codes O21, O21.0, O21.1, O21.2, O21.8 and O21.9). All O21 diagnoses were chosen to be included in both outpatient visits and inpatient episodes, to reduce selection bias possibly caused by broader or more stringent diagnostic or hospitalization criteria applied in different health care units.

In **Study I**, incidence of HG was calculated by comparing the number of pregnancies diagnosed with HG and resulting in delivery to the number of all pregnancies resulting in delivery during the study period. The association between HG and maternal, environmental, and pregnancy-related factors were evaluated by comparing 1) case women's HG pregnancies to reference women's pregnancies and 2) case women's HG pregnancies to their non-HG pregnancies.

In **Study II**, the number of outpatient visits and hospitalizations due to HG were calculated per 10,000 woman-years. Multiple visits or hospitalizations of the same person on the same date were calculated as one. Duration of hospitalization was calculated as days. A daytime visit in the hospital was calculated as one day, and an overnight hospitalization as two days. The number of outpatient visits and hospitalizations, as well as the total number of days spent in a hospital, were calculated per pregnancy. To account for duration of pregnancy, the number of admissions were calculated per pregnancy weeks in those pregnancies for which the information was available, i.e. pregnancies resulting in delivery and pregnancy terminations; gestational week is not recorded in the FHDR in miscarriages, and duration of the condition in gestational trophoblastic disease or ectopic pregnancy is not recorded. Readmission rates in live births, stillbirths, gestational trophoblastic disease, ectopic pregnancies, miscarriages, and pregnancy terminations were compared to the total readmission rate. In pregnancies for which the data were available, i.e. pregnancies resulting in delivery, the association between readmissions and maternal, environmental, and pregnancy-related factors were evaluated. Pregnancies involving only one outpatient visit or hospitalization (no readmission) were compared to pregnancies involving more than one outpatient visit and/or hospitalization.

In **Study III**, the first HG pregnancy of each woman was chosen as an index pregnancy. To calculate the average recurrence rate of HG, all pregnancies following the index pregnancy were divided into those with a HG diagnosis and those without a HG diagnosis. To assess the chronological occurrence of pregnancies with HG diagnosis and pregnancies without HG diagnosis after the index pregnancy, and to

calculate the frequency of each combination, a recurrence pattern chart of HG was compiled.

Maternal, environmental, and pregnancy-related factors associated with recurring HG were analysed in two parts: index pregnancy comparisons and subsequent pregnancy comparisons: 1) Index pregnancies of women with recurring HG were compared to index pregnancies of women without recurring HG to identify factors which could predict HG recurrence in the future based on the woman's first HG pregnancy. 2) The following pregnancies with HG were compared to following pregnancies without HG to identify factors differentiating pregnancies with recurring HG from pregnancies without recurring HG.

In **Study IV**, the main outcome variables were the numbers of deliveries, pregnancy terminations and sterilizations during the study period. Pregnancy termination ratios were calculated as pregnancy terminations/1000 deliveries. The number of pregnancies and the percentage of women with at least one termination were calculated in each group. Differences in the outcomes, as well as maternal age, gravidity, and parity at time of sterilization, were compared between the study groups.

Data were collected using Finnish health care registers: Hospital Discharge Register (FHDR), Medical Birth Register (FMBR), Register of Induced Abortions, and Register of Sterilisations. The population of interest in the study were women diagnosed with HG. Case and reference women and main comparisons are presented in **Table 5**.

The data were compiled incrementally. The first data set was employed for analysis of recurrence of HG in following pregnancies (**Study III**). The initial set-up of the first data set, a matched case-control design, did not allow comprehensive analysis of factors affecting the risk of HG, and a population-scale data set was thus collected, including all pregnancies resulting in delivery in Finland. The extended data set was employed for analysis of incidence of HG (**Study I**), burden of illness caused by HG (**Study II**), association of HG with family planning (**Study IV**), and factors associated with HG (**Studies I**, **II** and **IV**).

STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines (Vandenbroucke et al., 2014) were followed in research and reporting of the study. The study plan was approved by the Ethical committee of Hospital District of Southwest Finland (43/180/2011), and the data were compiled with permission of the Finnish Institute for Health and Welfare (THL/658/5.05.00/2012; THL/372/5.05.00/2018). The legal basis for processing of personal data is public interest and scientific research according to Finnish legislation and European Union General Data Protection Regulation 2016/679 (GDPR), Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6.

Table 5. Overview of the study.

Hyperemesis gravidarum in Finland

Study I	Study II	Study III	Study IV
Focus & working title			
Incidence	Burden of illness	Recurrence	Family planning
Aims			
To evaluate the incidence of HG in Finland, and to assess factors associated with HG	To measure the need of hospitalizations and outpatient care of HG in Finland, and to assess factors associated with recurring hospitalizations and outpatient visits	To estimate the recurrence rate of HG in Finland, and to assess factors associated with HG recurring in following pregnancies	To evaluate the effect of HG on family planning: deliveries, pregnancy terminations and sterilizations
Case women			
Women with HG diagnosis in at least one pregnancy resulting in delivery	Women with HG diagnosis in any pregnancy	Women with HG diagnosis in more than one pregnancy resulting in delivery	Women with HG diagnosis in any pregnancy
Reference women			
Women never diagnosed with HG	n/a	n/a	Women never diagnosed with HG
Main comparisons			
Case women's pregnancies diagnosed with HG vs 1) Case women's pregnancies without HG 2) Reference women's pregnancies without HG	Case women's pregnancies involving more than one HG diagnoses vs Case women's pregnancies with only one HG diagnosis	Case women's HG pregnancies following an HG pregnancy vs Case women's non-HG pregnancies following an HG pregnancy	Case women's deliveries, pregnancy terminations and sterilisations vs Reference women's deliveries, pregnancy terminations and sterilisations
Outcomes			
Incidence of HG	Outpatient visits Hospitalizations Readmission rate of HG in the same pregnancy Recurrent hospitalizations due to HG in the same pregnancy	Recurrence rate of HG in following pregnancies	Deliveries Pregnancy terminations Sterilizations

4.3 Main outcomes

Main outcomes of the study are summarized above in **Table 5**. To assess these outcomes, data were collected from the registers described below.

4.4 Data collection

HG case women were identified using the FHDR. Data about deliveries and maternal, environmental, and pregnancy-related factors in all pregnancies resulting in delivery were obtained from the FMBR. Pregnancy termination data were collected from the Finnish Register of Induced Abortions, and sterilization data from the Finnish Register of Sterilisations (**Table 6**).

Data linkage between registers was performed by the Finnish Institute for Health and Welfare using each woman's personal identity code, and the data were delivered to the researchers without identification data. Regarding offspring, the year and month of delivery were obtained, permitting chronological analysis of pregnancies without disclosing the children's birth dates.

Table 6. Health care registers used in the data collection.

Register	Studies	Variables
Finnish Hospital Discharge Register	**I, III, IV**	Diagnoses and diagnosis dates: HG Exclusion diagnoses: Other conditions causing nausea or vomiting (gastroenteritis, ICD-10 K29; appendicitis, ICD-10 K35; gallstones, ICD-10 K80; pancreatitis, ICD-10 K85)
	II	Diagnoses and diagnosis dates: HG, miscarriage, ectopic pregnancy, gestational trophoblastic disease Exclusion diagnoses: as above
Finnish Medical Birth Register	**I–IV**	Maternal, environmental, and pregnancy-related factors at the time of each pregnancy: maternal age, gravidity, parity, pre-pregnancy BMI, smoking status, marital status, socioeconomic status based on maternal occupation, municipality population, ART, number of fetuses, sex of fetus(es) Time-related variables: year and month of delivery
Finnish Register of Induced Abortions	**I, II, IV**	Pregnancy termination (I, II, IV); pregnancy termination date (I, II, IV); duration of the pregnancy up to the day of the procedure (II)
Finnish Register of Sterilisations	**IV**	Sterilization; sterilization date

Study participant selection flowchart is presented in **Figure 7**. **Studies I, II** and **IV** focused on the same data set from different points of view, whereas in **Study III**, the

first to be published, an earlier data set was used. In all studies, women with at least one pregnancy resulting in delivery during the study period were included. Case women were defined as women diagnosed with HG in at least one pregnancy. In **Studies I, II and IV**, 5 case women's pregnancies were excluded due to other causes of vomiting. In **Study III**, focusing on recurrence of HG in following pregnancies, women with only one pregnancy and women with no pregnancies after their first HG pregnancy were excluded, as well as pregnancies with HG diagnosis only in late pregnancy or other causes of vomiting.

4.4.1 Study I

All women who had one or more pregnancies resulting in delivery between years 2005 and 2017 in the FMBR were included in the study. Women who had at least one pregnancy diagnosed with HG in the FHDR were chosen as cases (N = 9,315) and other women (N = 428,150) as the reference group. The case women had altogether 17,934 pregnancies. The case women's pregnancies with HG diagnosis (N = 9,549) were compared to their pregnancies without HG diagnosis (N = 8,385) and to the reference women's pregnancies (N = 723,453).

4.4.2 Study II

All pregnancies (N = 10,392) with HG discharge diagnosis (in the FHDR between years 2005 and 2017 were included in the study, regardless of the outcome. Admissions and outpatient visits with HG discharge diagnosis were included in the analyses. The outcomes were determined by combining the HG diagnosis data with other register data: information about deliveries was drawn from the FMBR, pregnancy termination data from the Register of Induced Abortions, and diagnoses of gestational trophoblastic disease, ectopic pregnancy and miscarriage were retrieved from the FHDR.

4.4.3 Study III

Study III was conducted with an earlier data set covering years 2004–2011. Women with pregnancies resulting in delivery and with an HG discharge diagnosis before gestational weeks 20+0 in the FHDR between years 2004 and 2011 were included in the study. Women who had only one pregnancy during the study period (N = 2,642) and women who did not have pregnancies after their first HG pregnancy (N = 885) were excluded.

4.4.4 Study IV

In **Study IV**, the case and reference group selection was similar with **Study I**. In addition to data about deliveries, **Study IV** also included pregnancy terminations and sterilizations. All pregnancy terminations and sterilization regardless of grounds for termination or sterilization were included in the analyses. To study the women with HG in more detail, two case subgroups were analysed in addition to the initial setting: To identify women affected by HG early in their reproductive history, women diagnosed with HG in their first identified pregnancy were selected (case subgroup I, N = 6,785), and to identify the most severe cases, women with more than one hospitalization due to HG in the same pregnancy (case subgroup II, N = 1,448) were selected.

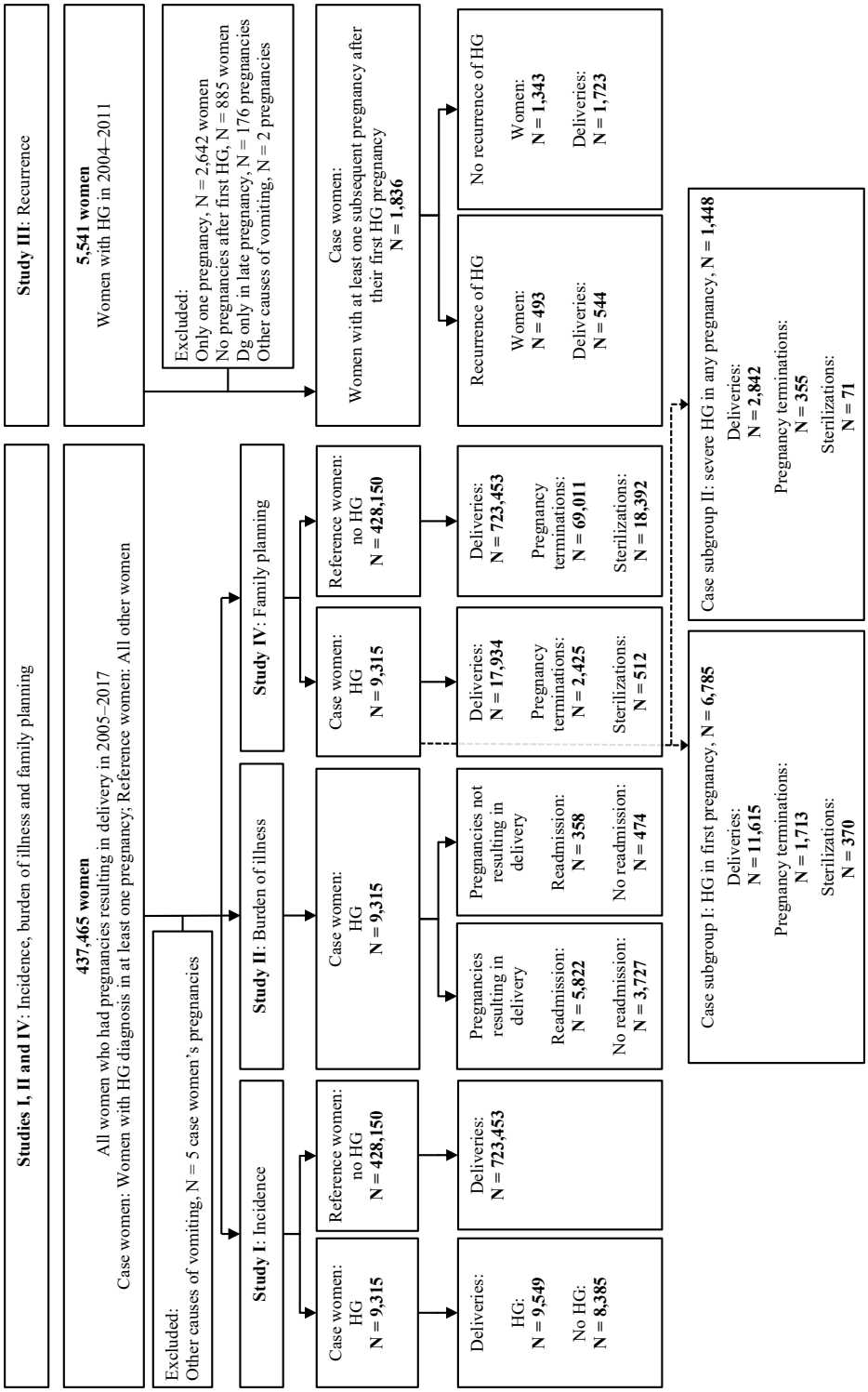

Figure 7. Flowchart of **Studies I–IV**.

4.5 Statistical methods

Methods are summarized in **Table 7**. To account for repeated pregnancies, generalised estimating equations were used when applicable. Results of comparisons were presented as incidence rate ratios (IRR) or odds ratios (OR) according to each comparison method. Statistical analyses were performed with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

Table 7. Methods used for calculation of study outcomes.

Study	Outcomes	Reported as	Methods
I	Incidence of HG	%	Number of pregnancies with HG divided by number of all deliveries
	Annual variation of incidence	IRR, 95% CI	Poisson regression
	Factors associated with HG	OR, 95% CI	Univariable and multivariable logistic regression
II	Outpatient visits due to HG	N	Number of outpatient visits due to HG
	Annual variation of outpatient visits due to HG	Annual values of outpatient visits/10,000 woman-years, P value	Poisson regression
	Hospitalizations due to HG	N	Number of hospitalizations due to HG
	Annual variation of hospitalizations due to HG	Annual values of hospitalizations/10,000 woman-years, P value	Poisson regression
	Readmission rate of HG	%	Number of pregnancies with more than one outpatient visit or hospitalization due to HG divided by the number of all HG pregnancies
	Multiple admissions due to HG in one pregnancy in different pregnancy outcomes	OR, 95% CI	Binary logistic regression
	Factors associated with multiple admissions	OR, 95% CI	Univariable and multivariable logistic regression
III	Recurrence rate of HG in following pregnancies	%	After case women's first HG pregnancy resulting in delivery, the number of pregnancies resulting in delivery and diagnosed with HG divided by number of all deliveries
	Factors associated with recurring HG	OR, 95% CI	Univariable and multivariable logistic regression

IV	Deliveries/woman, case vs reference women	IRR, 95% CI	Poisson regression
	Pregnancy terminations/1000 women, case vs reference women	IRR, 95% CI	Poisson regression
	Sterilizations/1000 women, case vs reference women	IRR, 95% CI	Poisson regression
	Women with at least one termination, case vs reference women	IRR, 95% CI	Log-binomial regression
	Mean age, gravidity and parity at sterilization	Mean±SD, P values	One-way ANOVA with Tukey's multiple comparison method

HG, hyperemesis gravidarum; IRR, incidence rate ratio; CI, confidence interval; OR, odds ratio; SD, standard deviation, ANOVA, analysis of variance.

In **Studies I, II** and **III**, the maternal, environmental, and pregnancy-related variables were categorized for the analysis as described in **Table 8** and compared according to the study settings.

Table 8. Units and categories of variables.

Variable	Unit	Categories
Maternal age	Years	≤20; 21–25; 26–30; 31–35; 36–40; ≥41
Gravidity	Pregnancies	1; 2; 3; 4; ≥5
Parity	Deliveries	1; 2; 3; 4; ≥5
Pre-pregnancy BMI	kg/m^2	<18.5; 18.5–24.9; 25–29.9; 30–34.9; ≥35
Smoking	n/a	No / Yes, but quit during the first trimester / Yes, continued smoking after the first trimester
Marital status	n/a	Living with partner / Not living with partner
Employment status	n/a	**Studies I** and **II**: Upper-level white-collar workers / White-collar workers / Blue-collar workers / At home (unemployed, retired, stay-at-home mother) / Other (entrepreneur, student, undetermined) **Study III**: Employed/Unemployed
Municipality population	Inhabitants	<10,000; 10,000–99,999; ≥100,000
ART	n/a	No/Yes
Number of fetuses	Fetuses	1; ≥2
Sex of fetuses	n/a	Singleton pregnancies: Male / Female Multiple pregnancies: All male / All female / Both sexes

BMI, body mass index; ART, assisted reproductive technology

Factors with a P value of <0.10 in univariable analysis were included in the multivariable models with the exception of socioeconomic status which was excluded from all multivariable analyses due to high proportion of missing data. In reporting the results, statistical significance was set at P<0.05. Missing data were not imputed.

5 Results

5.1 Incidence of HG

Average incidence of HG in pregnancies resulting in delivery in 2005–2017 in Finland was 1.3%. In terminated pregnancies, incidence of HG was 0.6%, and combined incidence of HG in pregnancies resulting in delivery and terminated pregnancies was 1.2%. The incidence was 1.3% in singleton pregnancies resulting in delivery and 2.9% in multiple pregnancies resulting in delivery.

The annual overall incidence varied during the study period between 1.2% (in 2011) and 1.5% (in 2016) with a minor increasing trend of 1 case/10,000 deliveries per year during the study period (IRR for 1-year increase = 1.01, P < 0.001, 95 % CI; 1.00 to 1.02) (**Figure 8**).

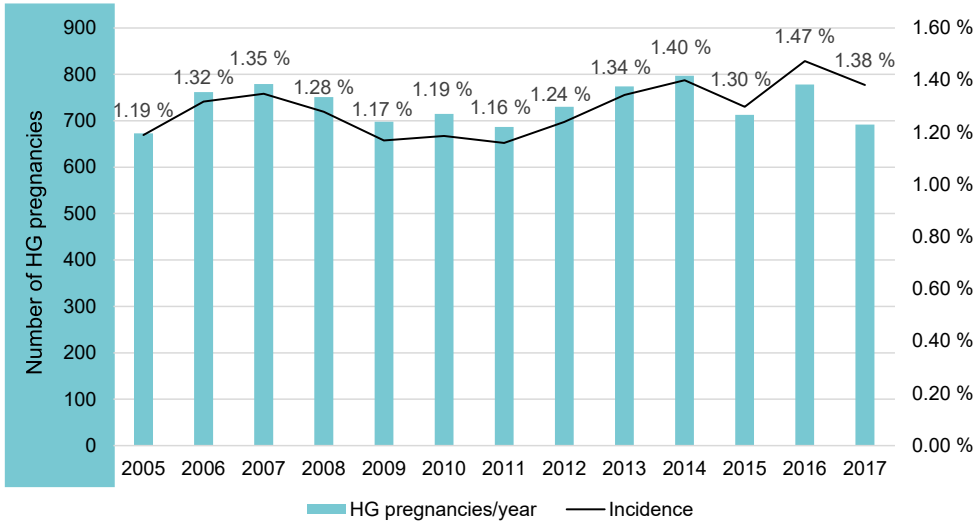

Figure 8. Number of HG pregnancies and annual incidence of HG in 2005–2017.

5.2 Outpatient care and hospitalizations

Altogether 16,853 outpatient visits and 9,101 hospitalizations due to HG occurred during the study period, with yearly averages of 1,296 outpatient visits and 700 hospitalizations. From 2005 to 2017, the number of outpatient visits increased by on average 45 visits/10 000 deliveries per year ($P < 0.0001$), and the number of hospitalizations decreased by on average 31 hospitalizations/10 000 deliveries per year ($P < 0.0001$) (**Figure 9**).

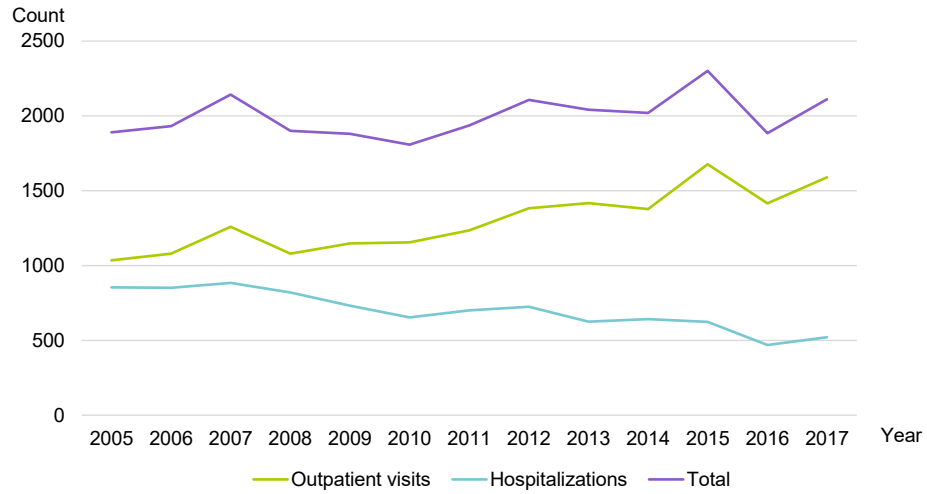

Figure 9. Outpatient visits and hospitalizations due to HG in Finland, 2005–2017.

The sum of outpatient visits or hospitalizations per pregnancy ranged from 1 to 35, with a median of two per pregnancy. The maximum number of outpatient visits per pregnancy was 32, and the maximum number of hospitalizations per pregnancy was 17. The length of hospitalizations ranged from 1 to 129, with a median of 3 days. Very long hospitalizations were rare; 10% of the hospitalizations were longer than ten days and 0.5% longer than one month. The number of outpatient visits and hospitalizations per one week of pregnancy was higher in terminated pregnancies than in pregnancies resulting in delivery. The majority of outpatient visits and hospitalizations occurred in the first trimester of pregnancy (**Figure 10**).

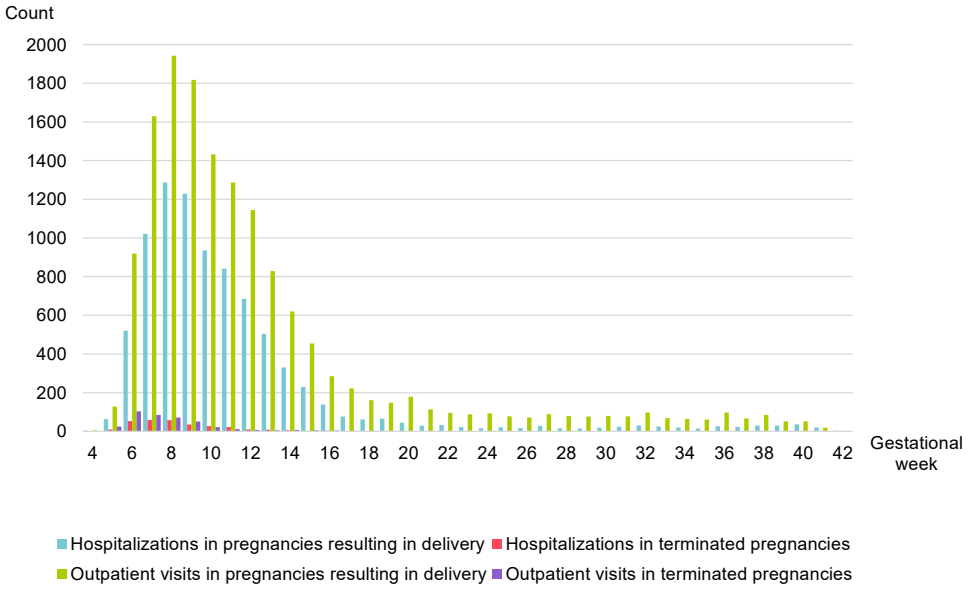

Figure 10. Total number of outpatient visits and hospitalizations by gestational week in 2005–2017.

5.3 Readmissions due to HG

Overall readmission rate (including both outpatient visits and hospitalizations) was 60% and rehospitalization rate was 17%. In comparison of pregnancy outcomes, overall readmission rate was highest in pregnancies resulting in live birth (61%) or stillbirth (61%) and lowest in miscarriages (40%) (**Table 9**). Ectopic pregnancies (N = 16) and cases of gestational trophoblastic disease (N = 8) were rare in HG pregnancies, and they were not included in the comparisons.

Table 9. Readmissions due to HG in different pregnancy outcomes

Outcome	HG pregnancies, readmission/total (readmission rate)	OR (95% CI)
Live birth	5,803/9,518 (61%)	Ref.
Stillbirth	19/31 (61%)	1.02 (0.50–2.09)
Miscarriage	121/299 (40%)	0.44 (0.34–0.55)
Pregnancy termination	230/509 (45%)	0.51 (0.43–0.61)
Total	6,180/10,381 (60%)	

HG, hyperemesis gravidarum; OR, odds ratio; CI, confidence interval. OR calculated using binary logistic regression.

Percentages of outpatient visits and hospitalizations in pregnancies resulting in delivery (N = 9,549) and not resulting in delivery (N = 808) are presented in **Figure 11**.

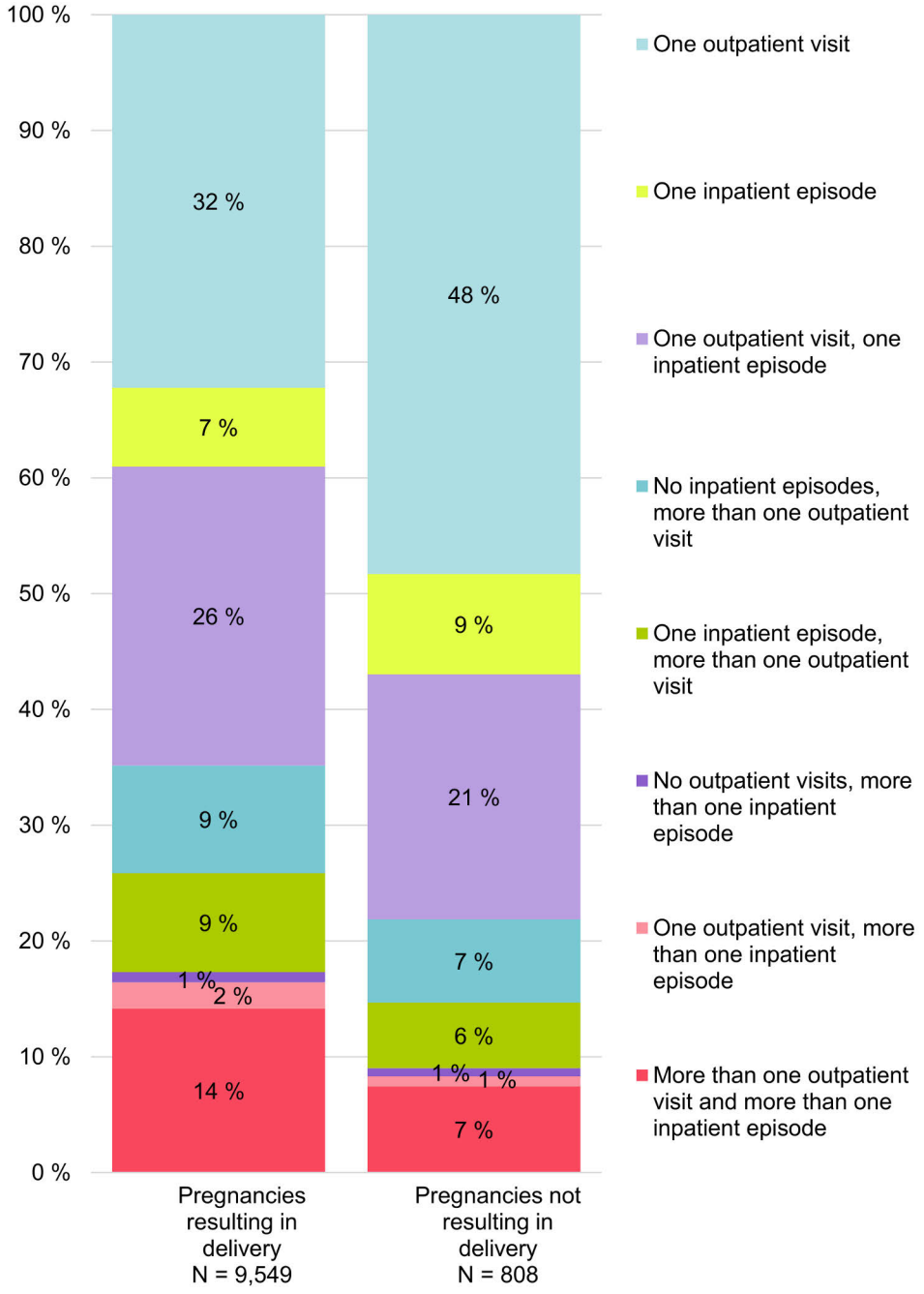

Figure 11. Readmissions by outpatient visits and hospitalizations due to HG in pregnancies resulting in delivery and pregnancies not resulting in delivery in 2005–2017.

5.4 Recurrence of HG

Recurrence of HG was analysed in pregnancies resulting in delivery. In the first dataset, 2004–2011, there were 1,836 women who had at least one subsequent pregnancy after their first HG pregnancy. They had 2,267 pregnancies resulting in delivery following their first HG pregnancy, and HG reoccurred in 544 of these pregnancies. The recurrence rate of HG was thus 24%. Approximately 5% of women who had more than two pregnancies resulting in delivery had HG in all of them. Patterns of HG and non-HG pregnancies are presented in **Figure 12**.

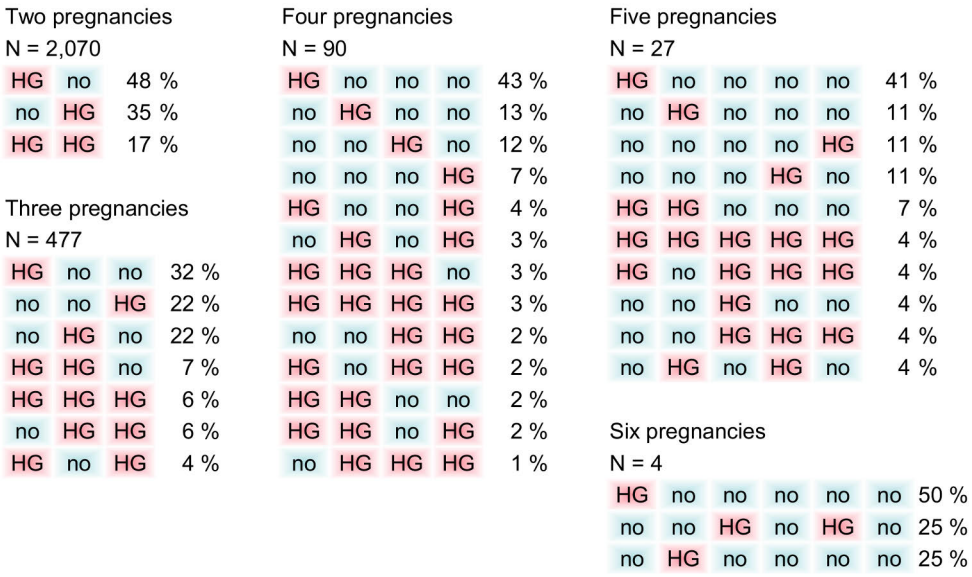

Figure 12. Recurrence patterns of HG in pregnancies resulting in delivery.

In the later data set, 2005–2017, there were 3,047 women who had at least one pregnancy resulting in delivery after their first HG pregnancy. In all, they had 5,066 subsequent pregnancies, and 1,125 of these pregnancies were diagnosed with HG. The recurrence rate of HG in this data set was thus 22%.

5.5 Family planning

Results regarding deliveries, pregnancy terminations and sterilizations are summarized in **Figure 13** and presented in more detail in **Table 10**.

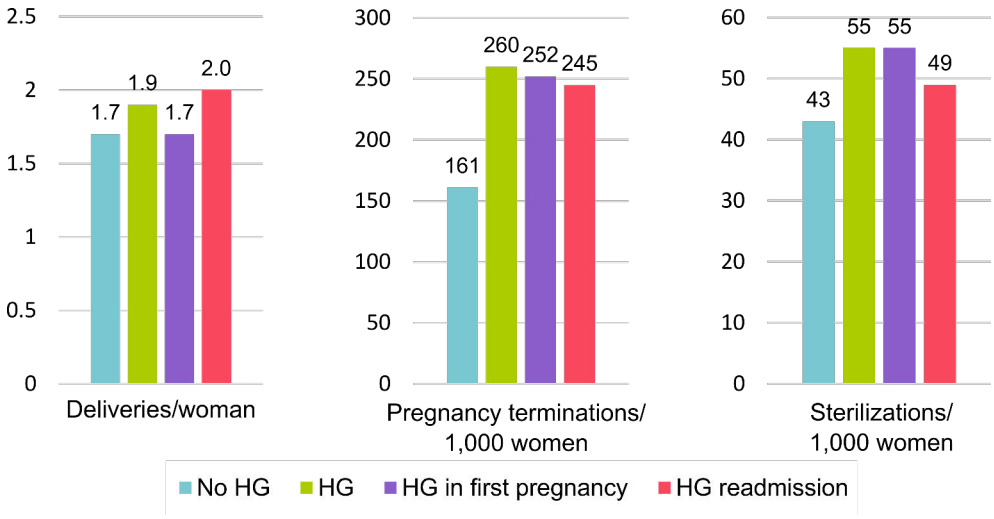

Figure 13. Deliveries, pregnancy terminations and sterilizations in each study group.

Table 10. Comparisons of deliveries, pregnancies, pregnancy terminations and sterilizations in each study group. All case groups were compared to reference group.

	No HG	HG	HG in first pregnancy	HG readmission
N	428,150	9,315	6,785	1,448
Deliveries/woman	1.7	1.9	1.7	2.0
IRR (95% CI)	Ref	1.09 (1.07–1.11)	0.99 (0.97–1.00)	1.11 (1.07–1.15)
Pregnancies/woman	1.9	2.2	2.0	2.2
IRR (95% CI)	Ref	1.12 (1.10–1.14)	1.03 (1.01–1.04)	1.13 (1.09–1.17)
Pregnancy terminations/1000 women	161	260	252	245
IRR (95% CI)	Ref	1.41 (1.35–1.46)	1.35 (1.25–1.45)	1.33 (1.20–1.47)
Pregnancy terminations/1000 deliveries	95	135	147	125
IRR (95% CI)	Ref	1.28 (1.23–1.33)	1.45 (1.38–1.52)	1.18 (1.06–1.31)
Women with at least one termination, N (%)	52,099 (12.2)	1678 (18.0)	1189 (17.5)	254 (17.5)
IRR (95% CI)	Ref	1.31 (1.26–1.37)	1.33 (1.26–1.40)	1.27 (1.14–1.42)
Sterilizations/1000 women	43	55	55	49
IRR (95% CI)	Ref	1.44 (1.32–1.58)	1.36 (1.23–1.51)	1.29 (1.02–1.63)

Age at sterilization, mean±SD	35.9±4.4	34.4±4.5	34.8±4.6	34.3±4.6
P value	Ref	<0.0001	<0.0001	0.008
Gravidity at sterilization, mean±SD	4.0±2.0	4.2±2.1	4.1±2.0	4.2±2.0
P value	Ref	0.120	0.929	0.782
Parity at sterilization, mean±SD	3.2±1.4	3.2±1.3	3.1±1.2	3.2±1.4
P value	Ref	0.879	0.529	0.415

HG, hyperemesis gravidarum; SD, standard deviation; IRR, incidence rate ratio; CI, confidence interval. IRRs calculated using log-binomial regression for women with at least one termination and using Poisson regression for other outcomes adjusted for maternal age at delivery. P values calculated with one-way analysis of variance using Tukey's multiple comparison method.

5.6 Factors associated with HG

Summary of factors associated with HG, readmission due to HG and recurrence of HG are presented in **Figure 14** to **Figure 18**. Numerical results are presented in detail in **Table 11** to **Table 16**.

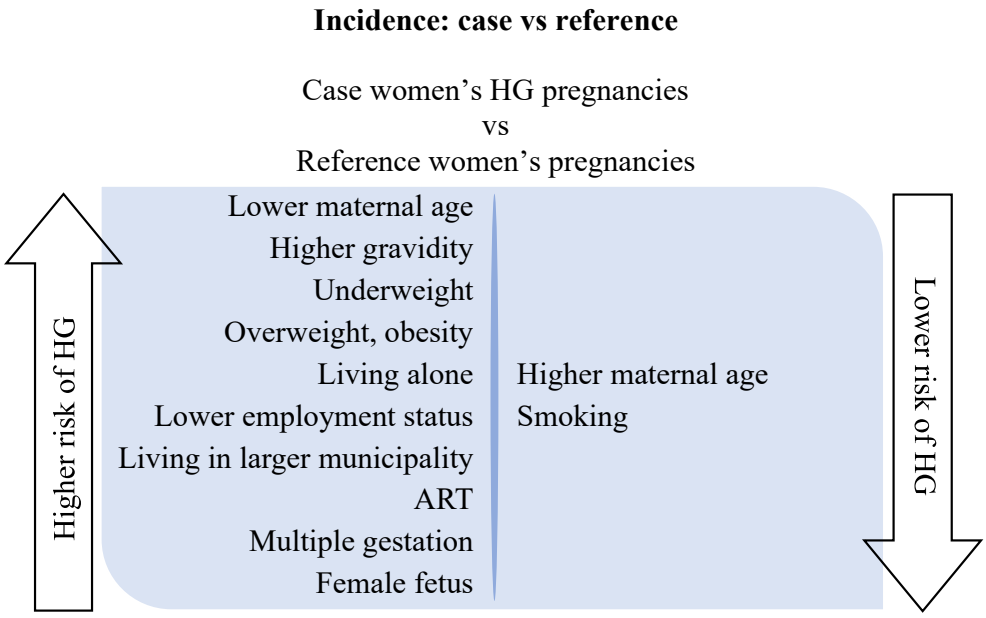

Figure 14. In **Study I**, factors associated with HG in comparison of case women's HG pregnancies and reference women's pregnancies.

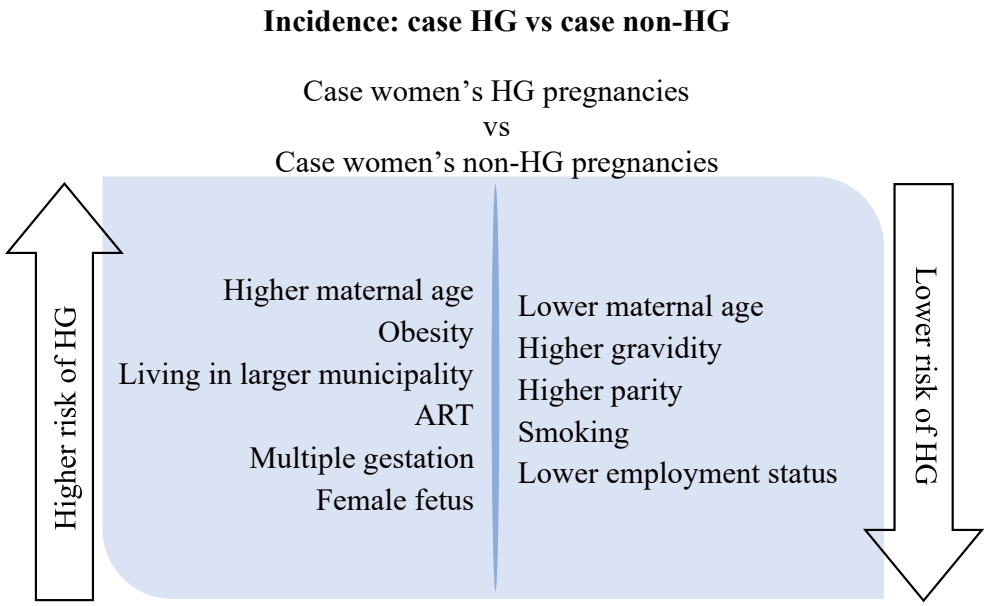

Figure 15. In **Study I**, factors associated with HG in comparison of case women's pregnancies diagnosed with HG and their pregnancies not diagnosed with HG.

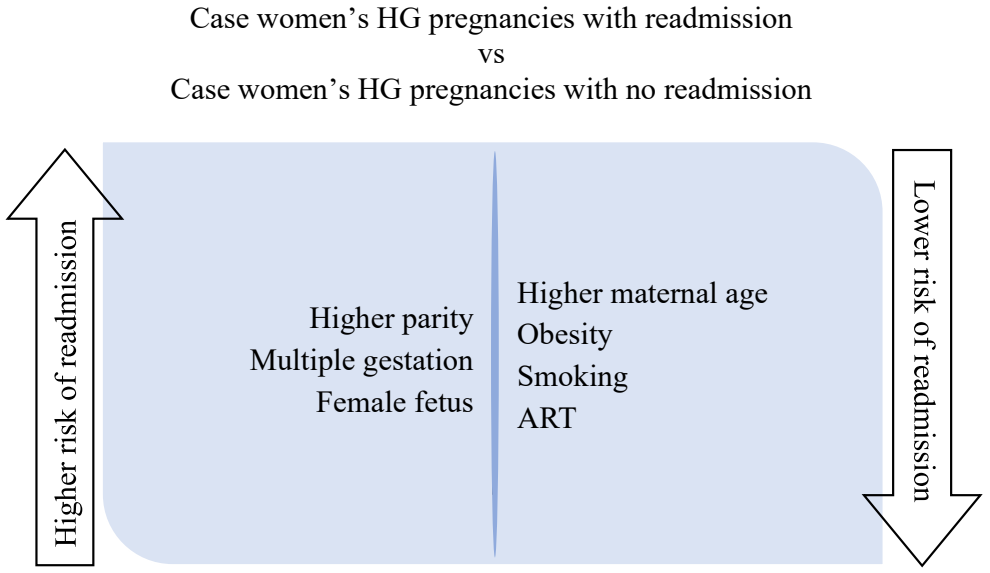

Figure 16. In **Study II**, factors associated with readmission due to HG in comparison of pregnancies with more than one outpatient visit or hospitalization due to HG and pregnancies with only one outpatient visit or hospitalization.

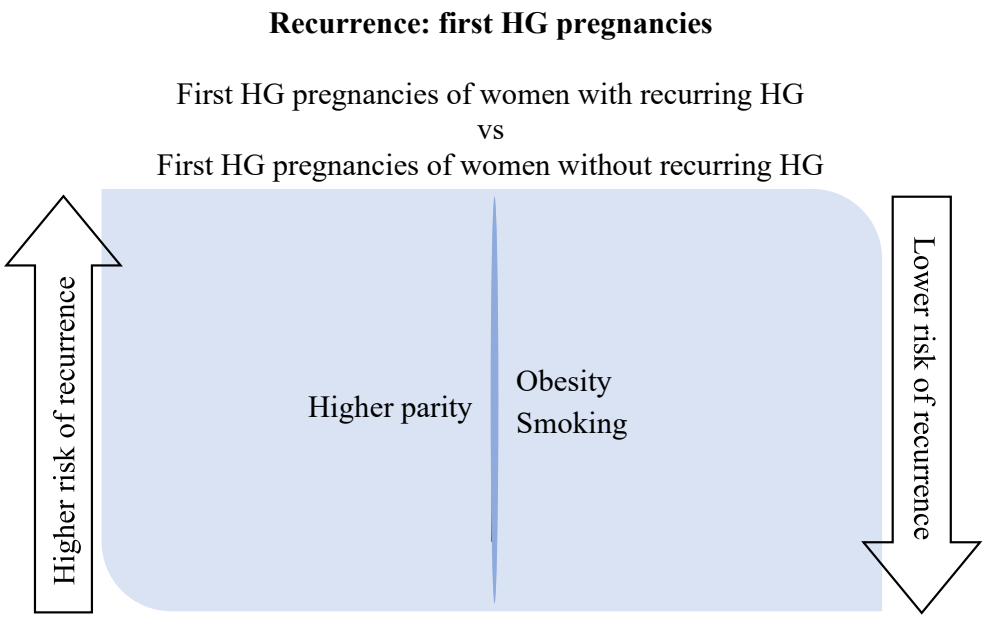

Figure 17. In **Study III**, factors associated with recurrence of HG in following pregnancies in comparison of first pregnancies diagnosed with HG of women who had recurrence of HG in at least one of their following pregnancies and women who did not have recurrence of HG.

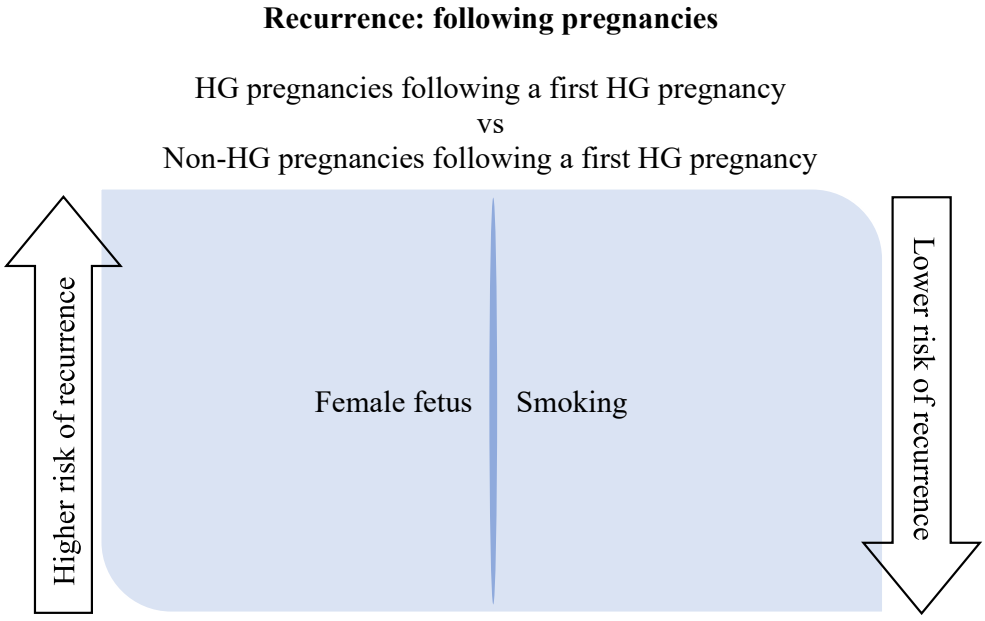

Figure 18. In **Study III**, factors associated with recurrence of HG in comparison of HG pregnancies following a first pregnancy diagnosed with HG and non-HG pregnancies following a first pregnancy diagnosed with HG.

5.6.1 Maternal factors

Detailed results regarding associations between maternal factors and HG are presented in **Table 11** and **Table 12**.

In comparison of case women's HG pregnancies and reference women's pregnancies, higher gravidity and parity, overweight and underweight were associated with higher risk of HG, whereas higher maternal age was associated with lower risk.

In comparison of case women's HG pregnancies and their non-HG pregnancies, higher maternal age and BMI ≥35 kg/m^2 were associated with higher risk of HG, whereas higher gravidity and parity were associated with lower risk.

In comparison of pregnancies with readmission due to HG and pregnancies without readmission due to HG, only parity of ≥5 was associated with higher risk of readmission due to HG, whereas higher maternal age and BMI ≥35 kg/m^2 were associated with lower risk of readmission.

Associations between maternal factors and recurrence of HG were minimal. Women whose first HG pregnancy occurred when they were expecting their 2nd child had marginally higher risk of recurrence of HG in their following pregnancies, and BMI of 30–34.9 kg/m^2 was associated with lower risk of recurrence.

Table 11. Maternal factors during pregnancy: frequencies and distribution in all study groups.

	Reference women	Case women/Study I: Incidence		Case women/Study II: Readmission		Case women/Study III: Recurrence			
	All pregnancies N = 723,453	HG pregnancies N = 9,549	Non-HG pregnancies N = 8,385	HG pregnancies with readmission N = 5,822	HG pregnancies without readmission N = 3,727	First HG pregnancies of women with recurring HG N = 493	First HG pregnancies of women without recurring HG N = 1,343	HG pregnancies after the first HG pregnancy N = 544	Non-HG pregnancies after the first HG pregnancy N = 1,723
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age: years									
≤20	29,018 (4.0)	568 (6.0)	473 (5.6)	337 (5.8)	231 (6.2)	48 (9.7)	117 (8.7)	13 (2.4)	28 (1.6)
21–25	129,956 (18.0)	2,228 (23.3)	2,071 (24.7)	1,321 (22.7)	907 (24.3)	154 (31.2)	445 (33.1)	106 (19.5)	390 (22.6)
26–30	241,766 (33.4)	3,176 (33.3)	2,949 (35.2)	1,975 (33.9)	1,201 (32.2)	190 (38.5)	506 (37.7)	194 (35.7)	643 (37.3)
31–35	214,044 (29.6)	2,449 (25.7)	2,077 (24.8)	1,526 (26.2)	923 (24.8)	76 (15.4)	218 (16.2)	161 (29.6)	491 (28.5)
36–40	91,792 (12.7)	960 (10.1)	706 (8.4)	563 (9.7)	397 (10.7)	22 (4.59)	52 (3.9)	62 (11.4)	142 (8.2)
≥41	16,877 (2.3)	168 (1.8)	109 (1.3)	100 (1.7)	68 (1.8)	3 (0.6)	5 (0.4)	8 (1.5)	29 (1.7)
Gravidity: number of pregnancies, current pregnancy included									
1	233,337 (32.3)	3,135 (32.9)	1,710 (20.4)	1,870 (32.1)	1,265 (33.9)	Gravidity not included in **Study III**			
2	217,204 (30.0)	2,729 (28.6)	2,279 (27.2)	1,686 (29.0)	1,043 (28.0)				
3	129,136 (17.9)	1,669 (17.5)	1,695 (20.2)	1,011 (17.4)	658 (17.7)				
4	66,150 (9.1)	925 (9.7)	1,050 (12.5)	567 (9.7)	358 (9.6)				
≥5	77,159 (10.7)	1,090 (11.4)	1,644 (19.6)	687 (11.8)	403 (10.8)				

Parity: number of pregnancies resulting in delivery, current pregnancy included									
1	303,018 (41.9)	4,265 (44.7)	2,357 (28.1)	2,545 (43.7)	1,720 (46.2)	314 (63.7)	908 (67.8)	n/a	n/a
2	244,370 (33.8)	3,047 (31.9)	3,006 (35.9)	1,864 (32.0)	1,183 (31.8)	112 (22.7)	261 (19.5)	293 (53.9)	937 (54.4)
3	105,261 (14.6)	1,367 (14.3)	1,599 (19.1)	851 (14.6)	516 (13.9)	32 (6.5)	89 (6.6)	146 (26.8)	444 (25.8)
4	36,185 (5.0)	473 (5.0)	703 (8.4)	292 (5.0)	181 (4.9)	17 (3.5)	37 (2.8)	55 (10.1)	176 (10.2)
≥5	34,175 (4.7)	394 (4.1)	713 (8.5)	268 (4.6)	126 (3.4)	18 (3.7)	45 (3.4)	50 (9.2)	166 (9.6)
Pre-pregnancy BMI: kg/m^2									
< 18.5	25,449 (3.6)	432 (4.8)	402 (4.9)	266 (4.7)	166 (4.6)	28 (6.5)	62 (5.1)	25 (4.8)	71 (4.3)
18.5–24.9	435,726 (62.3)	5,363 (58.23)	4,703 (57.8)	3,286 (58.3)	2,077 (57.7)	275 (63.8)	747 (60.9)	312 (59.4)	920 (55.3)
25–29.9	152,360 (21.8)	2,076 (22.4)	1,812 (22.4)	1,277 (22.7)	799 (22.2)	89 (20.7)	272 (22.2)	113 (21.5)	403 (24.2)
30–34.9	57,602 (8.2)	905 (9.7)	806 (10.0)	552 (9.8)	353 (9.8)	21 (4.9)	102 (8.3)	48 (9.1)	185 (11.1)
≥ 35	28,615 (4.1)	462 (4.9)	396 (5.0)	254 (4.5)	208 (5.8)	18 (4.2)	44 (3.6)	27 (5.1)	86 (5.2)

HG, hyperemesis gravidarum; BMI, body mass index.

Table 12. Results of comparisons of **maternal factors** during pregnancy.

	Study I: Incidence		**Study II:** Readmission	**Study III:** Recurrence	
	Case women's HG pregnancies vs reference women's pregnancies[1]	Case women's HG pregnancies vs their non-HG pregnancies[1]	Case women's HG pregnancies with readmission vs their HG pregnancies without readmission[2]	First HG pregnancies of women with recurring HG vs first HG pregnancies of women without recurring HG[3]	Case women's HG pregnancies after the first HG pregnancy vs their non-HG pregnancies after the first HG pregnancy[4]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, years					
≤20	1.94 (1.77–2.12)	0.88 (0.76–1.02)	1.04 (0.85–1.27)	1.09 (0.75–1.59)	1.51 (0.74–3.09)
21–25	1.44 (1.38–1.52)	0.90 (0.83–0.97)	0.92 (0.82–1.04)	0.92 (0.72–1.18)	1.03 (0.79–1.35)
26–30	Ref	Ref	Ref	Ref	Ref
31–35	0.79 (0.75–0.82)	1.22 (1.13–1.32)	0.97 (0.87–1.09)	0.93 (0.68–1.27)	1.10 (0.86–1.40)
36–40	0.66 (0.61–0.70)	1.59 (1.42–1.78)	0.81 (0.70–0.95)	1.13 (0.67–1.91)	1.35 (0.96–1.90)
≥41	0.56 (0.48–0.66)	1.95 (1.50–2.53)	0.86 (0.60–1.21)	1.60 (0.38–6.75)	0.82 (0.34–1.99)
Gravidity: number of pregnancies, current pregnancy included					
1	Ref	Ref	Ref	Gravidity not included in **Study III**	
2	1.11 (1.07–1.15)	0.60 (0.55–0.66)	1.07 (0.97–1.19)		
3	1.23 (1.16–1.29)	0.47 (0.43–0.52)	1.02 (0.91–1.15)		
4	1.41 (1.32–1.51)	0.41 (0.36–0.46)	1.04 (0.90–1.21)		
≥5	1.60 (1.48–1.73)	0.28 (0.25–0.31)	1.13 (0.98–1.30)		

Parity: number of pregnancies resulting in delivery, current pregnancy included					
1	Ref	Ref	Ref	Ref	n/a
2	0.98 (0.95–1.00)	0.52 (0.48–0.56)	1.03 (0.93–1.14)	1.33 (1.00–1.76)	Ref
3	0.98 (0.93–1.03)	0.43 (0.40–0.48)	1.12 (0.98–1.28)	1.13 (0.71–1.80)	1.03 (0.84–1.3)
4	0.98 (0.91–1.06)	0.36 (0.32–0.41)	1.14 (0.93–1.40)	1.40 (0.73–2.69)	1.01 (0.75–1.4)
≥5	0.94 (0.85–1.04)	0.29 (0.25–0.34)	1.41 (1.11–1.78)	1.02 (0.53–1.95)	1.02 (0.73–1.4)
Pre-pregnancy BMI: kg/m^2					
< 18.5	1.21 (1.10–1.34)	0.96 (0.83–1.10)	1.05 (0.85–1.29)	1.38 (0.85–2.22)	0.91 (0.55–1.51)
18.5–24.9	Ref	Ref	Ref	Ref	Ref
25–29.9	1.15 (1.09–1.21)	1.04 (0.97–1.12)	1.01 (0.91–1.13)	0.93 (0.70–1.23)	0.80 (0.63–1.03)
30–34.9	1.33 (1.24–1.43)	1.07 (0.97–1.19)	1.01 (0.87–1.17)	0.58 (0.35–0.96)	0.77 (0.54–1.11)
≥ 35	1.41 (1.28–1.56)	1.16 (1.01–1.33)	0.77 (0.63–0.93)	1.32 (0.74–2.38)	0.91 (0.56–1.48)

HG, hyperemesis gravidarum; BMI, body mass index; OR, odds ratio; CI, confidence interval. ORs calculated with multivariable logistic regression analysis, factors with $p < 0.10$ in univariable analysis included in the multivariable model, specifically:

[1] Included in the multivariable model: age, gravidity, pre-pregnancy BMI, smoking, marital status, municipality population, ART, number of fetuses and sex of the fetus.

[2] Included in the multivariable model: age, parity, BMI, smoking, ART, number of fetuses and sex of the fetus.

[3] Included in the multivariable model: parity, BMI, smoking, and municipality population.

[4] Included in the multivariable model: age, BMI, smoking, municipality population, ART, and the sex of the fetus.

5.6.2 Environmental factors

Detailed results regarding associations between environmental factors and HG are presented in **Table 13** and **Table 14**.

In comparison of case women's HG pregnancies and reference women's pregnancies, living alone, lower employment status and higher municipality population were associated with higher risk of HG. In comparison of case women's HG pregnancies and their non-HG pregnancies, higher municipality population was associated with higher risk of HG.

Lower employment status was associated with lower risk of HG in comparison of case women's HG pregnancies and their non-HG pregnancies, as well as with lower readmission risk. Smoking was associated with lower risk of HG, readmissions and recurrence in all comparisons.

Table 13. Environmental factors during pregnancy: frequencies and distribution in all study groups

	Reference women	Case women/**Study I**: Incidence		Case women/**Study II**: Readmission		Case women/**Study III**: Recurrence			
	All pregnancies N = 723,453	HG pregnancies N = 9,549	Non-HG pregnancies N = 8,385	HG pregnancies with readmission N = 5,822	HG pregnancies without readmission N = 3,727	First HG pregnancies of women with recurring HG N = 493	First HG pregnancies of women without recurring HG N = 1,343	HG pregnancies after the first HG pregnancy N = 544	Non-HG pregnancies after the first HG pregnancy N = 1,723
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Smoking during pregnancy									
No	596,643 (84.7)	8,350 (89.7)	7,129 (87.7)	5,213 (91.7)	3,137 (86.6)	460 (95.4)	1,158 (88.3)	512 (96.8)	1,499 (90.2)
Yes, 1st	40,475 (5.7)	448 (4.8)	385 (4.7)	236 (4.1)	212 (5.9)	12 (2.5)	54 (4.1)	5 (0.9)	51 (3.1)
Yes, cont.	67,150 (9.5)	511 (5.5)	615 (7.6)	238 (4.2)	273 (7.5)	10 (2.1)	99 (7.6)	12 (2.3)	112 (6.7)
Marital status: living with partner									
Yes	650,552 (94.5)	8,516 (93.8)	7,546 (93.5)	5,220 (93.5)	3,296 (94.1)	464 (95.7)	1,236 (94.8)	507 (96.2)	1,619 (96.4)
No	38,184 (5.5)	566 (6.2)	520 (6.4)	361 (6.5)	205 (5.9)	21 (4.3)	68 (5.2)	20 (3.8)	60 (3.6)
Employment status									
Upper-level white collar	102,012 (21.9)	959 (16.5)	776 (15.1)	634 (17.4)	325 (15.4)	In **Study III**, employment status reported as: 1) Employed; 2) Unemployed/at home			
White collar	189,595 (40.7)	2,377 (41.1)	2,051 (39.7)	1,450 (39.8)	927 (43.9)				
Blue collar	75,167 (16.1)	852 (14.7)	800 (15.6)	518 (14.2)	334 (15.8)	1) 272 (73.9)	801 (76.1)	293 (83.7)	968 (81.3)
At home	25,413 (5.5)	422 (7.8)	493 (9.4)	287 (7.9)	135 (6.4)	2) 96 (26.1)	252 (23.9)	57 (16.3)	222 (18.7)
Other	73,602 (15.8)	1,143 (19.9)	1,047 (20.2)	751 (20.6)	392 (18.6)				
Municipality population									
<10,000	122,886 (17.1)	1,333 (13.9)	1,452 (17.5)	799 (13.7)	534 (14.4)	223 (45.2)	551 (41.1)	238 (43.8)	628 (36.5)
10,000–99,999	322,268 (44.8)	4,062 (42.5)	3,697 (44.5)	2,471 (42.6)	1,591 (42.9)	196 (39.8)	536 (39.9)	216 (39.7)	748 (43.4)
≥100,000	274,496 (38.1)	4,118 (43.6)	3,178 (38.0)	2,536 (43.7)	1,582 (42.7)	74 (15.0)	255 (19.0)	90 (16.5)	347 (20.1)

HG, hyperemesis gravidarum.

Table 14. Results of comparisons of **environmental factors** during pregnancy.

	Study I: Incidence		**Study II:** Readmission	**Study III:** Recurrence	
	Case women's HG pregnancies vs reference women's pregnancies[1]	Case women's HG pregnancies vs their non-HG pregnancies[1]	Case women's HG pregnancies with readmission vs their HG pregnancies without readmission[2]	First HG pregnancies of women with recurring HG vs first HG pregnancies of women without recurring HG[3]	Case women's HG pregnancies after the first HG pregnancy vs their non-HG pregnancies after the first HG pregnancy[4]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Smoking during pregnancy					
No	Ref	Ref	Ref	Ref	Ref
Yes, 1st	0.70 (0.64–0.76)	1.05 (0.92–1.21)	0.67 (0.55–0.81)	0.55 (0.28–1.07)	0.32 (0.14–0.76)
Yes, cont.	0.44 (0.40–0.48)	0.85 (0.75–0.96)	0.54 (0.44–0.65)	0.27 (0.13–0.54)	0.38 (0.21–0.71)
Marital status: living with partner					
Yes	Ref	Ref	Ref	Ref	Ref
No	1.11 (1.03–1.21)	1.01 (0.89–1.14)	1.12 (0.94–1.34)	0.82 (0.50–1.36)	1.02 (0.60–1.74)
Employment status[5]					
Upper-level white collar	Ref	Ref	Ref	In **Study III**, employment status reported as:	
White collar	1.35 (1.25–1.46)	0.92 (0.83–1.02)	0.80 (0.68–0.94)	1) Employed;	
Blue collar	1.22 (1.11–1.35)	0.84 (0.74–0.94)	0.80 (0.66–0.97)	2) Unemployed/at home	
At home	1.81 (1.61–2.03)	0.67 (0.57–0.78)	1.08 (0.85–1.38)	1) Ref	Ref
Other	1.65 (1.51–1.80)	0.86 (0.77–0.97)	0.98 (0.82–1.18)	2) 1.12 (0.85–1.47)	0.84 (0.61–1.15)
Municipality population					
<10,000	Ref	Ref	Ref	Ref	Ref
10,000–99,999	1.19 (1.11–1.27)	1.15 (1.06–1.25)	1.03 (0.91–1.17)	1.21 (0.87–1.67)	1.10 (0.81–1.48)
≥100,000	1.47 (1.37–1.57)	1.31 (1.20–1.42)	1.05 (0.93–1.20)	1.21 (0.87–1.67)	1.33 (0.99–1.80)

HG, hyperemesis gravidarum; OR, odds ratio; CI, confidence interval. ORs calculated with multivariable logistic regression analysis, factors with $p < 0.10$ in univariable analysis included in the multivariable model, specifically:

[1] Included in the multivariable model: age, gravidity, pre-pregnancy BMI, smoking, marital status, municipality population, ART, number of fetuses and sex of the fetus.

[2] Included in the multivariable model: age, parity, BMI, smoking, ART, number of fetuses and sex of the fetus.

[3] Included in the multivariable model: parity, BMI, smoking, and municipality population.

[4] Included in the multivariable model: age, BMI, smoking, municipality population, ART, and the sex of the fetus.

[5] Employment status excluded from the multivariable analysis due to high proportion of missing data.

5.6.3 Pregnancy-related factors

Detailed results regarding associations between pregnancy-related factors and HG are presented in **Table 15** and **Table 16**.

In comparison of case women's HG pregnancies and reference women's pregnancies, as well as in comparison of case women's HG pregnancies and their non-HG pregnancies, ART, female fetus and multiple gestation were associated with higher risk of HG.

In comparison of pregnancies with readmission due to HG and pregnancies without readmission due to HG, female fetus and multiple gestation were associated with higher risk of readmission, whereas ART was associated with lower risk.

In comparisons regarding recurrence of HG, differences were minimal: only female fetus was associated with higher risk of recurrence of HG in comparison of recurring HG pregnancies after an initial HG pregnancy and pregnancies without recurring HG after an initial HG pregnancy.

Table 15. Pregnancy-related factors during pregnancy: frequencies and distribution in all study groups.

	Reference women	Case women/**Study I**: Incidence		Case women/**Study II**: Readmission		Case women/**Study III**: Recurrence			
	All pregnancies N = 723,453	HG pregnancies N = 9,549	Non-HG pregnancies N = 8,385	HG pregnancies with readmission N = 5,822	HG pregnancies without readmission N = 3,727	First HG pregnancies of women with recurring HG N = 493	First HG pregnancies of women without recurring HG N = 1,343	HG pregnancies after the first HG pregnancy N = 544	Non-HG pregnancies after the first HG pregnancy N = 1,723
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ART									
No	706,218 (97.6)	9,223 (96.6)	8,251 (98.4)	5,640 (96.9)	3,583 (96.1)	1,294 (96.4)	475 (96.4)	528 (97.1)	1,699 (98.6)
Yes	17,235 (2.4)	326 (3.4)	134 (1.6)	182 (3.1)	144 (3.9)	24 (3.6)	16 (3.6)	16 (2.9)	24 (1.4)
Number of fetuses									
1	713,163 (98.6)	9,244 (96.8)	8,310 (99.1)	5,612 (96.4)	3,632 (97.4)	483 (98.0)	1,294 (96.4)	532 (97.8)	1,700 (98.7)
≥2	10,290 (1.4)	305 (3.2)	75 (0.9)	210 (3.6)	95 (2.6)	10 (2.0)	24 (3.6)	12 (2.2)	23 (1.3)
Sex of the fetus, all pregnancies									
Male	370,094 (51.2)	4,388 (46.0)	4,359 (52.0)	2,612 (44.9)	1,776 (47.6)	228 (46.3)	606 (45.1)	268 (49.3)	931 (54.0)
Female	353,331 (48.8)	5,161 (54.0)	4,026 (48.0)	3,210 (55.1)	1,951 (52.4)	265 (53.75)	737 (54.9)	276 (50.7)	792 (46.0)
Sex of the fetus, singleton pregnancies									
Male	364,888 (51.2)	4,266 (46.1)	4,321 (52.0)	2,531 (45.1)	1,735 (47.8)	224 (46.4)	594 (45.1)	264 (49.6)	921 (54.2)
Female	348,249 (48.8)	4,978 (53.9)	3,989 (48.0)	3,081 (54.9)	1,897 (52.2)	259 (53.6)	723 (54.9)	268 (50.4)	779 (45.8)
Sex of the fetus, multiple gestation									
All male	3,445 (33.5)	71 (23.3)	31 (41.3)	45 (21.4)	26 (27.4)	2 (22.2)	8 (32.0)	1 (9.1)	8 (36.4)
All female	3,368 (32.7)	122 (40.0)	21 (28.0)	86 (41.0)	36 (37.9)	4 (44.4)	11 (44.0)	6 (54.5)	5 (22.7)
Both sexes	3,477 (33.8)	112 (36.7)	23 (30.7)	79 (37.6)	33 (34.7)	3 (33.3)	6 (24.0)	4 (36.4)	9 (40.9)

HG, hyperemesis gravidarum; ART, assisted reproductive technology.

Table 16. Results of comparisons of **pregnancy-related factors** during pregnancy.

	Study I: Incidence		**Study II:** Readmission	**Study III:** Recurrence	
	Case women's HG pregnancies vs reference women's pregnancies[1]	Case women's HG pregnancies vs their non-HG pregnancies[1]	Case women's HG pregnancies with readmission vs their HG pregnancies without readmission[2]	First HG pregnancies of women with recurring HG vs first HG pregnancies of women without recurring HG[3]	Case women's HG pregnancies after the first HG pregnancy vs their non-HG pregnancies after the first HG pregnancy[4]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ART					
No	Ref	Ref	Ref	Ref	Ref
Yes	1.47 (1.33–1.63)	1.44 (1.21–1.71)	0.77 (0.61–0.97)	1.00 (0.58–1.74)	1.74 (0.88–3.47)
Number of fetuses					
1	Ref	Ref	Ref	Ref	Ref
≥2	2.04 (1.83–2.28)	2.90 (2.28–3.68)	1.64 (1.27–2.12)	1.05 (0.50–2.19)	1.59 (0.77–3.29)
Sex of the fetus, all pregnancies					
Male	Ref	Ref	Ref	Ref	Ref
Female	1.20 (1.16–1.24)	1.26 (1.18–1.34)	1.13 (1.04–1.23)	0.93 (0.71–1.22)	1.29 (1.06–1.56)
Sex of the fetus, singleton pregnancies					
Male	Ref	Ref	Ref	Ref	Ref
Female	1.18 (1.15–1.22)	1.24 (1.17–1.32)	1.12 (1.03–1.21)	0.95 (0.77–1.17)	1.26 (1.04–1.51)
Sex of the fetus, multiple gestation					
All male	Ref	Ref	Ref	Ref	Ref
All female	1.66 (1.27–2.16)	2.52 (1.39–4.60)	1.31 (0.71–2.44)	1.45 (0.21–9.98)	1.94 (0.25–15.02)
Both sexes	1.49 (1.14–1.95)	2.12 (1.16–3.90)	1.32 (0.70–2.48)	2.00 (0.25–15.99)	6.93 (1.19–40.41)

HG, hyperemesis gravidarum; ART, assisted reproductive technology; OR, odds ratio; CI, confidence interval; ART, assisted reproductive technology. ORs calculated with multivariable logistic regression analysis, factors with $p < 0.10$ in univariable analysis included in the multivariable model, specifically:

[1] Included in the multivariable model: age, gravidity, pre-pregnancy BMI, smoking, marital status, municipality population, ART, number of fetuses and sex of the fetus.

[2] Included in the multivariable model: age, parity, BMI, smoking, ART, number of fetuses and sex of the fetus.

[3] Included in the multivariable model: parity, BMI, smoking, and municipality population.

[4] Included in the multivariable model: age, BMI, smoking, municipality population, ART, and the sex of the fetus.

5.7 Summary of main results

Main results of the study are presented in **Table 17**.

Table 17. Main results regarding HG in Finland.

Study	Outcome		Results
I	Incidence of HG		1.3%
II	Outpatient visits due to HG		1,296 outpatient visits/year
	Hospitalizations due to HG		700 hospitalizations/year
	Readmission rate of HG in one pregnancy; including both outpatient visits and hospitalizations		60%
	Rehospitalization rate of HG in one pregnancy		17%
III	Recurrence rate of HG in following pregnancies		1st data set, 2004–2011: 24% 2nd data set, 2005–2017: 22%
IV	Deliveries	women with HG	1.9 deliveries/woman
		without HG	1.7 deliveries/woman
	Pregnancy terminations	with HG	260 terminations/1000 women
		without HG	161 terminations/1000 women
	Sterilizations	with HG	55 sterilizations/1000 women
		without HG	43 sterilizations/1000 women

HG, hyperemesis gravidarum.

6 Discussion

The present study was the first to investigate the incidence and various aspects of HG in Finland. In spite of the relative rarity of HG, the burden caused by the condition was substantial with more than a thousand outpatient visits and several hundred hospitalizations due to HG each year. A change from inpatient treatment towards outpatient treatment was observed: frequency of hospitalizations decreased, whereas frequency of outpatient visits increased during the study period. Among women who were once diagnosed with HG, risk of HG in subsequent pregnancies was higher than in the general population: HG reoccurred in almost every fourth following pregnancy. HG appeared to have a partial effect on family planning: women with HG had more pregnancy terminations and sterilizations compared to women without HG. However, they had more deliveries, suggesting that HG may not decrease the total number of deliveries on the population level.

As for associative factors such as age and parity, the finding that HG pregnancies were different both compared to pregnancies of women who had never had HG and non-HG pregnancies of women who had HG in another pregnancy was novel and interesting, and partly explains why some factors have yielded opposite results in different previous studies: the comparison settings really matter. Predicting recurrence of HG in following pregnancies is difficult: analysis of associative factors revealed very few differences between HG survivors, and hence, these factors are not prognostic for HG in subsequent pregnancies.

6.1 Methodological considerations

As described in the Introduction, this thesis is part of a larger study involving several data sources. Initially, it was estimated that health care registers would be only a limited part of the sources, but during the study process it became obvious that the health care registers contain extensive amounts of information relevant to HG previously unexplored and unpublished in Finland. Thus, the choice of focusing on register data permitted in-depth analysis of the detailed data contents.

Register data also permits population-level research; when studying a relatively rare disease, sufficient statistical power is difficult to attain by other methods. This was tested first-hand, as the initially planned setup of the first data set, a matched

case-control design, did not allow thorough analysis of all background factors of interest in all study settings. The matched setting was discarded, and the first data set was used exclusively for analysing recurrence of HG in following pregnancies (**Study III**). The final population-scale data set included all pregnancies resulting in delivery in Finland, the study period was extended to cover years 2005–2017, and **Studies I**, **II** and **IV** were performed using the extended data set. The population-level approach permitted reliable detection of differences between study groups, and the large number of women with HG allowed pertinent subgroup analyses from different points of view. On the whole, concentrating on register data in this first doctoral thesis about HG in Finland proved to be fruitful: the study settings revealed results unattainable in small-scale case-control comparisons.

6.1.1 Definition of HG

As presented in the review of the literature, it was not until 2019 that consensus definition of HG was formulated (Jansen et al., 2021), and there is considerable divergence of definition of HG between studies performed thus far. In addition, practical considerations affect the use of definition of HG in different studies. The consensus definition contains elements not currently collected in registers and can thus mainly be implemented in clinical trials and other prospective studies. The definition of HG used in the present study was based on clinical diagnosis of HG following the ICD-10, as the classification was used in health care in Finland during the study period. Thus, the presence of HG diagnosis was decided by each treating physician by their judgement of the woman's condition evaluated using the diagnostic criteria. Register data are restricted to diagnosed HG cases in hospitals and outpatient clinics, and uniform application of diagnostic criteria and registering practices are important for register data quality. As the ICD-10 classification was well established and applied consistently in Finland during the study period, the diagnoses in our study can be considered rather reliable.

6.1.2 Inclusion and exclusion criteria

The inclusion and exclusion of study participants are illustrated in **Figure 7**, flowchart of the study. As no consensus about the definition of HG had not yet been reached until 2019, different inclusion and exclusion criteria have been applied in different studies, complicating comparisons between studies (Grooten et al., 2016). For instance, late-onset nausea and vomiting may be caused by other reasons than HG and has thus often been excluded from the studies, but the cut-off for determining when nausea and vomiting should be considered late-onset has not been uniform: some authors have referred to the first trimester (Louik et al., 2006), others have set

the limit earlier in the first trimester, e.g. to gestational week 9 (Goodwin, 1998) or 10 (Firoz et al., 2010; Matsuo et al., 2007), or extended the limit even until gestational week 24 (Fell et al., 2006) or 25 (Owe et al., 2019; Vikanes et al., 2010), while others have not posed any limits to the timing of the symptoms (Roseboom et al., 2011). World Health Organization has changed its HG time frame, too: in 2010, the International Classification of Diseases (ICD-10) defined the late vomiting diagnosis (O21.2) as "Excessive vomiting starting after 22 completed weeks of gestation" (World Health Organization, 2012), whereas the 2016 version of the ICD-10 defined late vomiting as "Excessive vomiting starting after 20 completed weeks of gestation" (World Health Organization, 2016). The consensus definition of HG presented in the third ICHG in 2019 mentions "Beginning of symptoms in early pregnancy", also leaving room for interpretation regarding timing of symptoms (Jansen et al., 2021).

The case group inclusion criteria were refined during the research process. In the first data set, late vomiting of pregnancy diagnoses (O21.2), and other HG diagnoses occurring after 20th gestational week were excluded in accordance with commonly used definition of HG as vomiting beginning before 20th week of gestation. However, further analysis of the data indicated that diagnosis code O21.2 was also found in instances of symptoms beginning earlier but persisting after 20 gestational weeks, leading to exclusion of data regarding these women. Patient experiences as described in support groups also indicated that although HG symptoms may have begun earlier, some women may not be diagnosed in early pregnancy, if they contact their health care provider only later, when they have already been ill for a prolonged period and can no longer cope at home. These aspects taken into consideration, the O21.2 diagnoses were chosen to be included in the updated data set in order not to misassign these women in the reference group.

In some studies, the O21.8 diagnosis, which primarily indicates vomiting due to another disease, is excluded (Bolin et al., 2013; Vandraas et al., 2013). However, it was observed that O21.8 diagnosis had also been employed in instances where no other cause of vomiting was diagnosed, as well as instances with diagnoses given on different days alternating between the other O21 diagnoses and O21.8. Thus, the O21.8 diagnoses were included in all of the substudies, as these women were considered to belong in the case group rather than in the reference group.

To rule out possible diagnostic misassignment, pregnancies with both HG and other nausea-related diagnoses were excluded from the case group. In the large data set these cases were extremely rare: only four cases of gallstones and one case of pancreatitis, indicating that the HG diagnoses in the data were fairly reliable.

6.1.3 Outcomes

Heterogeneity of outcomes across different studies impedes comparison of results, and to enhance comparability, core outcome sets have been defined for certain diseases. A core outcome set for HG research has been elaborated as a result of long-term international collaboration between HG researchers, clinicians, HG patients and other stakeholder groups (M. S. Fejzo, 2020; Jansen et al., 2019). However, as the core outcome set has been designed mainly for clinical trials, its usability in register-based data is limited. Items included in the core outcome set are presented in **Table 18**.

Table 18. Domains and items selected in an international consensus study for defining a core outcome set for HG research (Jansen et al., 2019). Items used in the present study are denoted in italics.

Domain	Items
Symptoms	Nausea Vomiting Inability to tolerate oral fluids or food Dehydration Weight difference
Laboratory findings	Electrolyte imbalances
Need for interventions to manage symptoms	Intravenous fluid treatment Use of additional medication
Maternal service utilisation	*Hospital treatment*
Maternal quality of life and wellbeing	Treatment compliance Patient satisfaction with treatment received Maternal physical and/or mental and/or emotional wellbeing Daily functioning
Maternal harm	Short term adverse effects of treatment Long-term adverse effects of treatment Maternal death
Pregnancy complications	Miscarriage Thrombosis and bleeding Hypertensive disorders Gestational diabetes
Termination of pregnancy	*Termination*[1] of a wanted pregnancy Considering termination of a wanted pregnancy
Birth outcomes	Babies born preterm Babies born small-for-gestational-age
Offspring outcomes	Congenital anomalies Offspring death; Fetal and neonatal mortality Neonatal morbidity; Hypoglycaemia and sepsis

[1] Pregnancy termination data with information about whether the pregnancy was wanted were not available in the register data in the present study.

In practice, selection of outcomes is restricted by the research context, in this case by the data contents of the registers available. In the register data, two of these outcomes were available for analysis: hospital treatment and pregnancy termination. However, it could be argued that as register data does not permit recognition of a wanted pregnancy, the pregnancy termination outcome intended in the core outcome set can only partially be analyzed using register data. In general, registers enable studying large numbers of individuals, unobtainable by other methods, but to attain a comprehensive picture of HG, combining several different register sources or complementing register data with prospectively collected patient data is needed.

6.1.4 Strengths and limitations

Main strengths and limitations of the study are summarized in **Figure 19**.

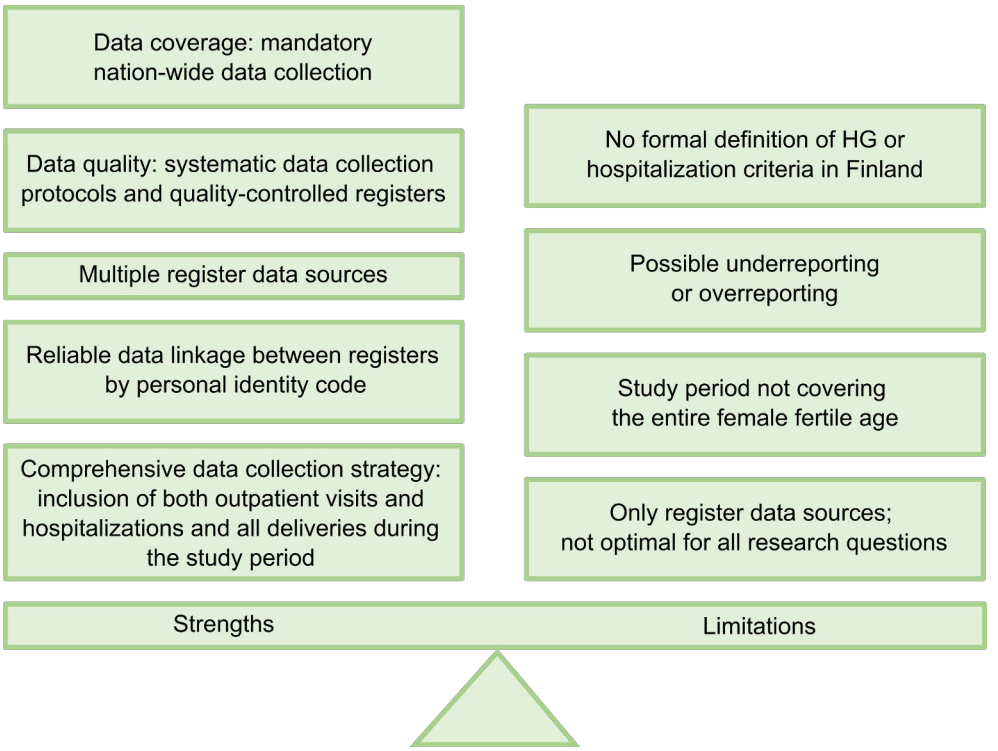

Figure 19. Strengths and limitations.

6.1.4.1 Strengths

Coverage and quality of Finnish health care registers are high (Sund, 2012; Heino et al., 2018). Health care registers are collected systematically throughout Finland into

centralized quality-controlled registers, data provision is obligatory, and all hospitals use the same data collection protocols established by the Finnish Institute for Health and Welfare (Gissler et al., 2010).

Using multiple register data sources allowed studying HG from several points of view. HG diagnoses derived from the FHDR formed the basis for selecting the case group and analyzing the numbers of outpatient visits and hospitalizations. The FMBR, with detailed follow-up data of pregnancies, provided valuable material for comparison of maternal, environmental, and pregnancy-related factors among women with or without HG, and the Register of induced abortions and the Sterilization register permitted discovery of novel results regarding family planning.

To fully take advantage of the registers, reliable linkage between registers is crucial. In the present study, data linkage was assured by using the personal identity code unique to each Finnish citizen and permanent resident. To ensure the study subjects' anonymity, the identity codes were replaced by identification numbers by the register keeper Finnish Institute of Health and Welfare before the data was handed out to the researchers. Thus, all hospitalizations, outpatient visits, deliveries, pregnancy terminations and other data compiled from different registers could be linked to each individual, permitting thorough analysis of their pregnancy-related conditions.

The comprehensive data collection strategy with HG diagnoses including both outpatient data and hospitalizations, as well as pregnancy terminations and sterilizations, provided abundant study material. The 13-year study period permitted analysis of several pregnancies of women who had more than one pregnancy in that time and to compare the case women's HG pregnancies not only with the reference women's pregnancies, but also with the case women's non-HG pregnancies, thus enabling evaluation of the effect of the maternal, environmental, and pregnancy-related factors.

6.1.4.2 Limitations

During the study period, there was no formal definition of HG available. In Finland, there are no official treatment guidelines or hospitalization criteria for HG, and thus treatment decisions are made by treating physicians according to each individual situation based on their symptoms, signs of dehydration, and laboratory tests such as ketonuria (Laitinen et al., 2019). General well-being or QoL of the patient may also be assessed and may affect admittance or discharge decisions. Considering this limitation, all O21 diagnoses in both outpatient visits and hospitalizations were included, thus reducing possible selection bias.

One of the most common limitations in register-based data is possible underreporting. Some instances of HG may not have been diagnosed, if, for example, some women who would have met diagnostic criteria did not seek medical care, or

if their symptoms had resolved by the time they had an appointment. As incidence and recurrence rates were determined based on pregnancies resulting in delivery, HG cases in terminated pregnancies were not included in the numbers. Thus, the observed rates can be considered a lower limit of the true incidence and recurrence. Overreporting of HG is unlikely but cannot be completely ruled out, as diagnostic practices may vary.

The study period, thirteen years, does not cover the entire female fertile age, and a longer follow-up time will be needed to assess the eventual effect of HG on the overall number of children a woman will have in her lifetime.

Using only register data sources restricted the possibility to analyse some aspects of HG. The register data do not include certain information, e.g. about the women's decision-making, thus not permitting analysis of possible causal effect of HG on family planning. Our data did not allow analysis of all factors previously reported to be associated with HG. For instance, based on strict non-discriminatory legislation, ethnicity, country of birth, or paternity are not available in the Finnish health care registers, and these factors could thus not be included in the analyses. The number of missing data about employment status was high.

In addition, register data are not always optimal for analysing some research questions, especially when a single variable is employed to represent complex situations. For instance, employment status, entered in the register as maternal occupation during pregnancy, was used as a surrogate variable to assess the women's socioeconomic status. This approach is not perfect, as even if a woman were registered e.g. as unemployed in the data, her income or socioeconomic status may not necessarily be low, if her unemployment was short-term, or if she had other financial sources. Similarly, data about living with or without a partner were used for assessing psychosocial support, even though living alone does not exclude other support networks. Keeping these limitations in mind, these variables were chosen with the assumption that in a large scale they can be presumed to reflect the conditions reasonably well. As some outcomes related to different aspects of HG, such as specific symptoms or laboratory test results, are not available in registers, they could not be included in the present study. In addition, data regarding other contraceptive methods besides sterilizations were not included.

6.2 Incidence of HG

The observed incidence, 1.3%, was close to incidences of HG reported in the other Nordic countries (Bolin et al., 2013; Vandraas et al., 2013). As discussed above in the context of definition of HG, variation between incidences reported in different studies across the world may at least partly stem from diversity in diagnostic criteria (Firoz et al., 2010; Goodwin, 1998), highlighting the need of universally accepted

diagnostic criteria (Grooten et al., 2016; Koot et al., 2018) Other reasons may be multiple ranging from different reporting or data systems to cultural or genetic differences (Firoz et al., 2010; Goodwin, 1998).

The small increase of annual incidence during the study period is similar to that found in a British study covering years 1998–2014 (Fiaschi et al., 2019) and a Norwegian study of years 1967–1998 (Trogstad et al., 2005). Incidences of HG varied over the years, being lowest in the beginning and higher towards the end of the study periods, possibly reflecting changes in diagnostic or registering practices over time and accross. This trend suggests that the necessity of medical care due to HG may be increasingly recognized and answered, corresponding to wishes expressed by women with NVP and HG (Havnen et al., 2019; Heitmann et al., 2016). Active antiemetic drug treatment may reduce the need of hospitalization, and better availability of antiemetic medication could thus fit the observed trend towards outpatient treatment.

6.3 Outpatient care and hospitalizations

Results regarding outpatient care and hospitalizations were in line with previous research: outpatient visits were more common than hospitalizations (Attard et al., 2002; Fiaschi et al., 2019), and mean number and length of hospitalizations were comparable to those found in other countries (Bacak et al., 2005; Bailit, 2005; Gazmararian et al., 2002; Koot et al., 2020; Tan et al., 2006).

The total annual number og HG cases remained rather stable, while the number of annual outpatient visits increased, and the number of hospitalizations decreased during the study period. This was a novel finding, and the rapidity and amplitude of the change suggest that it is likely to correspond to health care objectives of providing accessible treatment near patients in outpatient units; changes in HG severity or need of medical care as such would be unlikely to happen during such a short period. In a previous study comparing inpatient and outpatient care, QoL, mean PUQE score, satisfaction with care, obstetric and neonatal outcomes and readmission rates were as good in outpatient care as inpatient care (McParlin et al., 2016). Furthermore, outpatient care has been calculated to be more affordable than hospitalizations, without damaging effectiveness of care as measured by quality adjusted life years (Murphy et al., 2016). Hence, the observed transition can be considered commendable, as long as availability of inpatient care when needed is not compromised.

In the present study, most of the outpatient visits and hospitalizations due to HG occurred in the first trimester. However, persisting need of care was not rare: in approximately one third of the pregnancies, outpatient visits and hospitalizations occurred after the first trimester and in nearly one tenth of pregnancies in the third

trimester. These results correspond to previous studies indicating that HG symptoms frequently continue until the latter half of pregnancy or even until delivery (Fejzo et al., 2009; Fiaschi et al., 2016; Mullin et al., 2012).

Duration of pregnancy in this data could only be accounted for in pregnancies resulting in delivery and in terminated pregnancies, as there was no information regarding pregnancy weeks in the other pregnancy outcomes (miscarriage, ectopic pregnancy, and gestational trophoblastic disease). Outpatient visits and hospitalizations were more frequent per pregnancy week in terminated pregnancies than in pregnancies resulting in delivery. It could be hypothesized that very severe HG, manifesting as frequent need of care, could affect pregnancy termination decisions, thus leading to the observed results. However, as causality cannot be inferred with the current data, further research with broader methods and a prospective study design will be needed to evaluate whether such connection exists.

6.4 Readmissions due to HG

The HG readmission rates observed in the present study, 60% of all HG pregnancies, 61% of pregnancies resulting in delivery and 43% in pregnancies not resulting in delivery, were higher compared to rates observed in earlier studies. In most of the earlier studies, only hospitalizations were included, with readmission rates ranging from 13% to 32%: in a study of 121,885 women with HG, nation-wide hospitalization data in the UK was analyzed and the readmission rate was 28% (Fiaschi et al., 2016); other studies included data from a single hospital such as a French study of 109 women and readmission rate of 13% (Chraibi et al., 2015), and a Malaysian study of 192 women and readmission rate of 20% (Tan et al., 2006), whereas in a Dutch study of 191 women, data were collected from several hospitals, and the readmission rate was 32% (Koot et al., 2020). One study of 113 women with HG analyzed emergency department visits in a single hospital in the USA, and their revisit rate was 34% (Sharp et al., 2016). The rehospitalization rate, 17%, was closer to earlier results, highlighting the effect of different inclusion and exclusion criteria between studies. HG symptom spectrum may affect the choice of health care services: very severe symptoms may need treatment options not available in outpatient clinics, and outpatient visits occurring after hospitalizations may also include follow-up visits with milder symptoms.

The lower readmission rates in pregnancies not resulting in delivery observed in the present thesis are likely to be mainly due to the shorter overall duration of pregnancy. As demonstrated in the analysis of outpatient visits and hospitalizations by gestational week, HG symptoms are not limited to the beginning of pregnancy, thus leading to accumulation of readmissions even until delivery in some pregnancies. In terminated pregnancies, readmission rate was lower compared to

readmission rate in pregnancies resulting in delivery, but when duration of pregnancy was accounted for, the number of outpatient visits and hospitalizations per week was higher in terminated pregnancies than in pregnancies resulting in delivery.

6.5 Recurrence of HG

In the present thesis, HG recurred in 24% of pregnancies following an initial HG pregnancy in the first data set, 2004–2011, and 22% in the updated data set, 2005–2017. Recurrence of HG was fairly common compared to the overall incidence of HG on the population scale, making previous HG pregnancy a major risk factor for HG in following pregnancies.

The recurrence rate was closer to earlier results of register studies (Fiaschi et al., 2016; Trogstad et al., 2005) than survey studies (Fejzo et al., 2011; Fejzo et al., 2012). The Norwegian register study was conducted before the present study, covering years 1967–1998, and the recurrence rate of HG was 15% (Trogstad et al., 2005). The British register study timing and results were reasonably similar to the present study, with a partly overlapping study period, 1997–2012, and a recurrence rate of 26% (Fiaschi et al., 2016). In both previous register studies by Trogstad et al. and Fiaschi et al., the first two consecutive pregnancies of each woman were analyzed, whereas in our study, all pregnancies during the study period were included in the analysis.

In the American retrospective survey of 57 women who had visited a HG support Internet site and been treated for HG with intravenous hydration in an earlier pregnancy, the recurrence rate of HG, 81%, was markedly higher than in the register studies (Fejzo et al., 2011; Fejzo et al., 2012). The high percentage in the survey may partly be explained by the study setting, as the recurrence of HG was self-reported, while the recurrence rate according to hospitalization, 39%, was somewhat closer to the results of register studies. As registers do not reveal details of the women's symptoms, it is difficult to directly compare recurrence rates in register and survey studies; pregnancy without an HG diagnosis does not mean a symptom-free pregnancy, and some of the women with no recurrent HG diagnosis in register studies may themselves consider having recurring HG. Thus, the different methods complement each other, with register studies providing a likely lower limit of the real recurrence.

Recurrence patterns of HG in more than two successive pregnancies have not been published earlier and the results of this thesis cannot thus be compared with previous observations. Analyzing several consecutive pregnancies provided informative novel insights: HG can occur in the first pregnancy, or later, and in the instance of more than two pregnancies, having only HG pregnancies is quite rare.

Non-HG pregnancies may also occur between HG pregnancies. For women with previous experience of HG and planning a new pregnancy, these results are both somewhat comforting and also slightly vexing: on one hand, HG does not recur in the majority of following pregnancies, but on the other hand, the recurrence patterns are diverse and unpredictable.

6.6 Family planning

The results regarding pregnancy terminations and sterilizations were in line with the hypothesis: women diagnosed with HG had more pregnancy terminations and sterilizations than women never diagnosed with HG. However, contrary to the hypothesis, women diagnosed with HG had more deliveries.

6.6.1 Deliveries

In previous surveys, up to three of every four women have reported hesitating to become pregnant again after having experienced HG (Fejzo et al., 2011; Heitmann et al., 2017). On the contrary, in the present thesis, women with HG had more pregnancies/woman compared to women without HG. This result suggests that HG may not reduce the overall number of deliveries on the population level. In the subgroup analysis, however, women who had HG in their first identified pregnancy had fewer deliveries than those diagnosed with HG in any pregnancy, suggesting that experiencing HG in the beginning of reproductive life may influence women's decisions regarding new pregnancies. Nevertheless, compared to women without HG, they had as many, not fewer, deliveries, and this eventual effect could not thus be detected on the population scale.

The results in the present study and the previous surveys cannot be directly compared, as the study settings differed in many respects. In the survey studies, women may have responded according to their initial feeling regarding new pregnancies, but as it is not known whether or not they eventually had further pregnancies, the definite effect of HG on the number of deliveries cannot be estimated. With the present study settings, women's thoughts and motivations regarding the number of children cannot be analyzed. In addition, to determine the eventual effect of HG on the overall number of children, studies covering women's complete fertile age would be needed.

6.6.2 Pregnancy terminations

The results concerning pregnancy terminations were in line with previous research; 3–15% of women suffering from HG or nausea and vomiting of pregnancy have

reported terminating a pregnancy due to HG. In an HG support web site survey of 808 women, 15% had terminated at least one pregnancy due to HG (Poursharif et al., 2007), and in another online survey of 5,016 women with severe nausea and vomiting in the UK, 4.9% reported having terminated a pregnancy due to HG (Nana et al., 2021). In an interview study of 3,201 callers to a pregnancy sickness telephone helpline, 3% reported having a pregnancy termination due to HG (Mazzotta et al., 2001), and in another telephone interview study of 107 women, 7% had terminated a pregnancy due to HG (Havnen et al., 2019).

HG and pregnancy terminations may share some risk factors such as young age, being single, or socioeconomically vulnerable situations, possibly affecting the womens' decisions. As the grounds for pregnancy termination in Finland are recorded only on a general level, it was not possible to identify how many of the terminations in the present study were related to HG, but the considerably higher numbers of pregnancy terminations in all subgroups of women with HG compared to women without HG indicate that HG is likely to have affected at least some of the terminations.

6.6.3 Sterilizations

The novel finding of sterilizations being more common among women with HG compared to women never diagnosed with indicates that HG may have an effect on women's decision to permanently avoid further pregnancies. Moreover, the lower age at sterilization among women with HG also implies their intentness on sterilization. However, as in the case of pregnancy terminations, the grounds for sterilization are registered only on a general level, not permitting analysis of individual motivations or causal inference between HG and sterilizations.

In general, female sterilization is not a very common method of contraception in Finland, and during the study period, the frequencies of different sterilization methods varied (**Figure 5**). Essure, a hysteroscopically inserted sterilization device, became the most popular sterilization method in Finland in 2012 due to the relative rapidity and ease of the device's insertion process. However, its usage began to rapidly decrease in 2015 due to adverse effects experienced by several women and it was retracted from the market in 2017–2018 by the manufacturer. As the proportion of sterilizations with Essure was lower among women with HG, 23%, than among the reference women, 27%, it appears that Essure was not particularly favoured among women with HG and the higher number of sterilizations among them was not related to availability of this method. In general, the number of female sterilizations has declined in Finland since the 1990s, while the number of male sterilizations has moderately increased, and currently, male sterilization is more common than female sterilization (Finnish Institute for Health and Welfare, 2020e).

However, for women with HG, female sterilization may be more desirable to exclude all possibility of pregnancy, not only in their current relationship but permanently.

Mode of delivery may affect the choices as well, since sterilization can be performed in association with cesarean delivery. In Finland, approximately 16% of births are cesarean deliveries (Zeitlin et al., 2021), and comparison of rates of cesarean delivery among women with HG and women without HG could sheld light on the eventual differences in mode of delivery and its effect on the observed difference in sterilization rates.

Other methods of contraception were not included in the study, and more comprehensive research regarding use of contraception will be needed to further elucidate reproductive choices of women with HG.

6.7 Factors associated with HG

In general, the differences between pregnancies of women with and without HG were more prominent than differences between pregnancies of various subgroups of women with HG. In comparisons of women with and without HG, the findings were generally in line with previous research. Regarding the other comparisons, there were fewer previous studies to compare with, and the results were more variable, revealing novel results and highlighting the importance of study settings. Regarding recurrence of HG in following pregnancies, it was observed that predicting recurrence risk based on a woman's first HG pregnancy was not feasible because there were only few differences between pregnancies of women with or without recurring HG.

6.7.1 Maternal factors

The maternal factors available for analysis in the register data were age, gravidity, parity, and BMI.

6.7.1.1 Age

To recap the results presented in the Results section, associations between maternal age and HG are summarized in **Figure 20**. All age groups were compared to the most common age group, 26–30 years. Depending on the comparison settings, the odds of HG varied with increasing maternal age. When HG pregnancies of women with HG were compared to pregnancies of women never diagnosed with HG, HG was more frequent in younger age groups. However, when HG pregnancies of women with HG were compared to their non-HG pregnancies, HG occurred more often in older age groups. Readmissions due to HG were more common at younger age, whereas age was not associated with recurrence of HG.

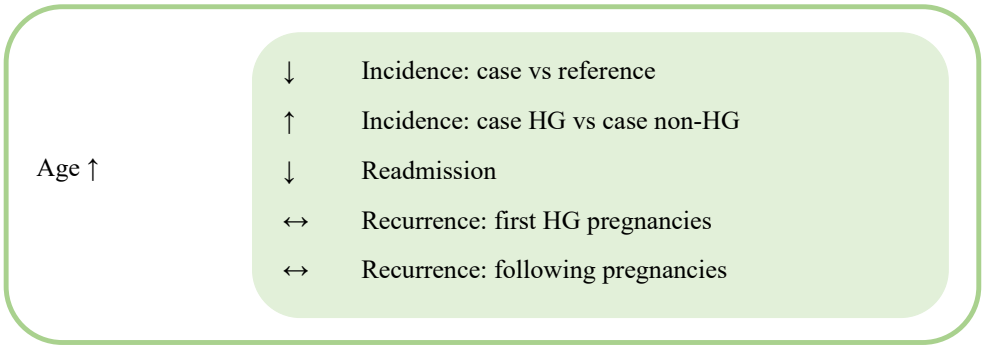

Figure 20. Association between increasing maternal age and HG. ↑ Increased odds, ↓ Decreased odds, ↔ No association

The results of the comparison between pregnancies of women with and without HG were in accordance with earlier studies. In a Canadian study of 157,922 deliveries, maternal age of younger than 20 years was associated with increased relative risk (RR) of HG compared to age group 20–29 years, and maternal age of more than 30 years was associated with decreased risk (Fell et al., 2006). In a study of 8,215,538 pregnancies in England, risk of HG was lower in age groups above 30 years (Fiaschi et al., 2016). In a Californian study of 520,739 pregnancies, average maternal age was lower among women with HG compared to women without HG (Bailit, 2005), and in a Norwegian cohort study, prevalence of HG was highest in age group of younger than 20 years (Vikanes et al., 2013). In a Norwegian population-based register study, prevalence of HG was highest in age group of 20–24 years (Vikanes et al., 2008). Thus, pregnancies with HG generally appear to occur at younger age (Bailit, 2005; Fell et al., 2006; Fiaschi et al., 2016; Vikanes et al., 2013).

The results about risk of readmission due to HG and recurrence of HG in following pregnancies were also in accordance with earlier results by Fiaschi et al.: risk of readmission due to HG was higher in younger age, whereas risk of recurrence was not associated with age.

However, the observation in the present study of HG being more common in older age groups when HG pregnancies of women who had HG in any pregnancy were compared to their non-HG pregnancies indicates that the association between age and risk of HG is not straightforward. The observation of elevated hCG levels during pregnancy in age groups below 25 years and over 35 years compared to ages between 25 and 35 years (Korevaar et al., 2015) is interesting in relation with these results. It thus appears that on the population level, HG tends to be more common at younger age, as observed in earlier studies, but among women who have had HG in any pregnancy, indicating a potential susceptibility of HG, possibly mediated by individual sensitivity to effects of hCG, the risk may actually increase with

increasing age. All in all, although associations between HG and age have been found, HG can occur at any age.

6.7.1.2 Gravidity and parity

The results about gravidity and HG are summarized in **Figure 21** and the results about parity and HG in **Figure 22**. In **Studies I, II** and **IV**, both gravidity and parity were included in the analysis. In **Study III**, only parity was analysed. Reference classes were gravity of 1 and parity of 1, except in comparison of recurrence of HG in following pregnancies, where other parity classes were compared to the lowest parity class, parity of 2.

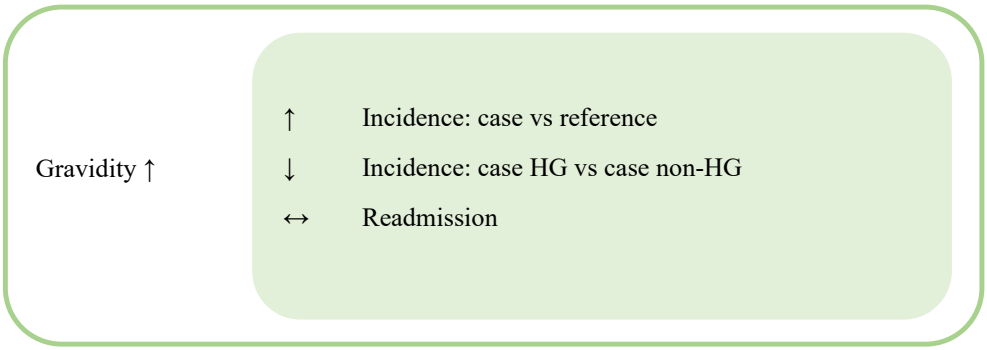

Figure 21. Association between increasing gravidity and HG. ↑ Increased odds, ↓ Decreased odds, ↔ No association

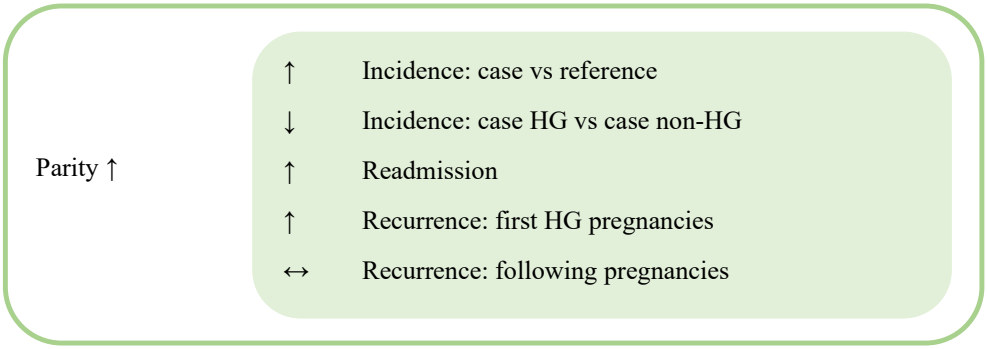

Figure 22. Association between increasing parity and HG. ↑ Increased odds, ↓ Decreased odds, ↔ No association

The results correspond to earlier studies, as both lower (Fell et al., 2006; Fiaschi et al., 2016; Roseboom et al., 2011) and higher (Kjeldgaard, Eberhard-Gran, Benth,

Nordeng et al., 2017; Vikanes et al., 2013; Vilming et al., 2001) gravidity or parity have been found to be associated with HG, and in some studies, no association has been found (Bailit, 2005; Matsuo et al., 2007). Based on these earlier observations and the detailed study settings, it appears that the relation between HG and gravidity and parity is indeed complex.

When comparing pregnancies of women with and without HG, the results that higher gravidity and parity were associated with increased risk of HG were similar with three Norwegian studies: a case-control study of 235 women covering years 1993–1997 (Vilming et al., 2001) and two studies reporting results of a cohort of 71,468 women in 1998–2008 (Kjeldgaard, Eberhard-Gran, Benth, Nordeng et al., 2017; Vikanes et al., 2013) but differed from a study of 157,922 deliveries in 1988–2002 in Canada (Fell et al., 2006), a study of 1,199,218 pregnancies in 2000–2006 in the Netherlands (Roseboom et al., 2011) and a study of 8,215,538 pregnancies in 1997–2012 in England (Fiaschi et al., 2016). All except one (Vilming et al., 2001) of these were population-based register studies. Inclusion and exclusion criteria in different studies may have affected the results; e.g., as the pregnancies in many studies were analysed in only two groups, HG vs non-HG pregnancies, it cannot be excluded that non-HG pregnancies of women who may have had HG in another pregnancy may have been included in the reference group.

However, the results may differ according to the study settings: in our study, when comparing HG pregnancies of women with HG to their non-HG pregnancies, higher gravidity and parity were associated with lower risk of HG. This is in line with the observation in Study III regarding recurrence patterns of HG, as most of the women had HG in their first pregnancy, but not in the following pregnancies, the risk of HG thus being highest in their first pregnancies compared to the following.

In some earlier studies, readmission risk due to HG was higher among nulliparous women,(Fiaschi et al., 2016; Godsey et al., 1991) but in others, neither age nor parity were associated with readmission risk.(Koot et al., 2020; Tan et al., 2006), whereas in one study, emergency department revisits were more common among HG patients with higher parity (Sharp et al., 2016). In the present study, increasing parity was associated with higher risk of readmission. The differences were small, and as gravidity did not show the same association, it could be hypothesized that this finding may not be related with parity as such, but could possibly be connected with the number of children the mother has, affecting her chances of getting rest at home. In survey and interview studies, women have expressed that HG strongly impedes their ability to take care of daily tasks, but as data regarding childcare conditions are not included in health care registers, this question cannot be further elucidated in the present study.

6.7.1.3 BMI

The results about the association of overweight and obesity with HG are compiled in **Figure 23** and the results regarding underweight in **Figure 24**. All BMI classes were compared to normal weight.

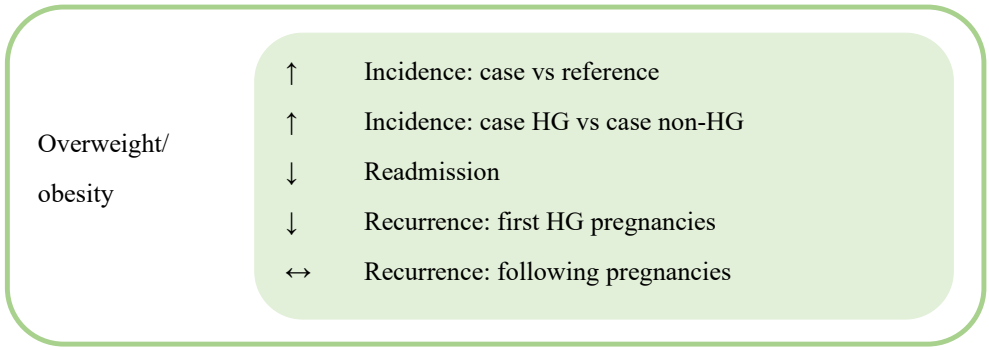

Figure 23. Association between overweight and/or obesity and HG. ↑ Increased odds, ↓ Decreased odds, ↔ No association

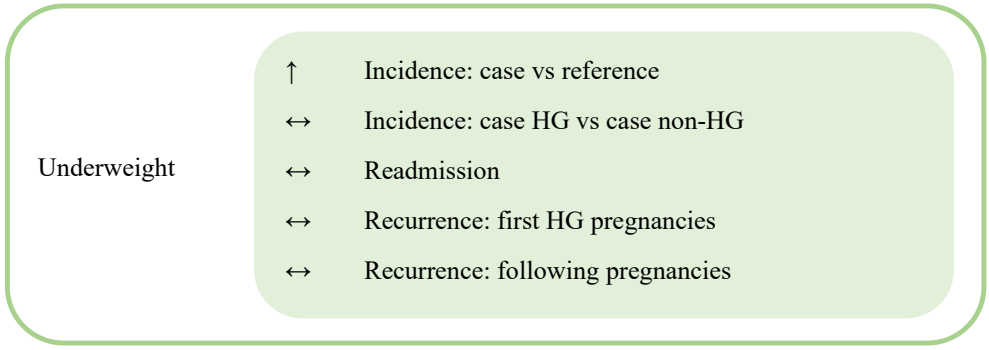

Figure 24. Association between underweight and HG. ↑ Increased odds, ↔ No association.

The results of comparison between the women with and without HG were in accordance with earlier studies: HG has been reported to be more common among under- or overweight women compared to normal weight (Lindholm et al., 2015; Matsuo et al., 2007; Vikanes et al., 2010). However, when comparing different pregnancies of women with HG, the associations were not as clear. Only BMI category ≥ 35 kg/m^2 was associated with higher risk of HG in comparison of HG pregnancies of women with HG and their non-HG pregnancies, whereas the same category was associated with lower risk of readmissions due to HG, and BMI 30–34.9 kg/m^2 in their first HG pregnancy was associated with lower risk of having HG

in following pregnancies. Underweight was not associated with HG in comparisons of different pregnancies of women with HG.

It thus appears that on the population scale, normal BMI is associated with lowest risk of HG in general, but among women with HG, possible changes of BMI from one pregnancy to another do not appear to be associated with the risk of HG in one direction or another.

6.7.2 Environmental factors

Environmental factors available for analysis in the register data were smoking, marital status, employment status, and municipality population.

6.7.2.1 Smoking

Compilation of results regarding associations between smoking and HG is presented in **Figure 25**.

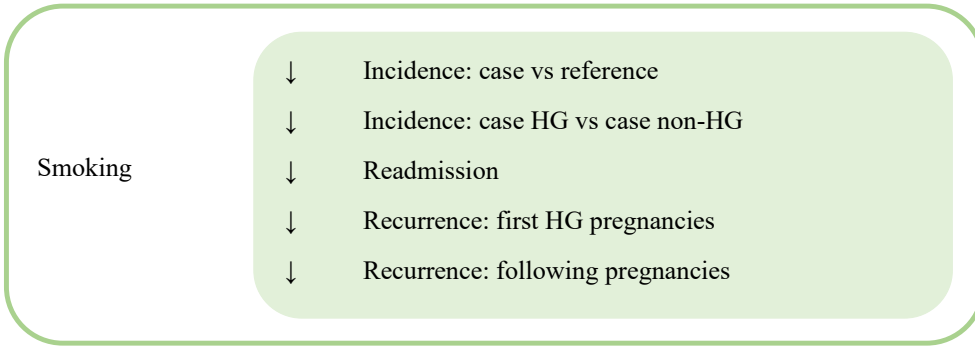

Figure 25. Association between smoking and HG. ↓ Decreased odds.

In accordance with earlier results, smoking was found to be associated with lower risk of HG, recurrence of HG and readmissions due to HG. In general, a minority of the women smoked: in 10% of pregnancies of women without HG, the women smoked until the 3rd trimester, whereas women with HG smoked until the 3rd trimester in 6% of their HG pregnancies and in 8% of their non-HG pregnancies. The association of smoking with the incidence of HG was apparent: HG occurred in 1.4% of smoke-free pregnancies, whereas in pregnancies involving smoking, incidence of HG was 0.9%. The 1.5-fold difference between the incidences was in line with earlier results of population-level studies where 0.9%–1.2% of non-smoking women and 0.6%–0.8% of women who reported smoking during pregnancy had HG (Fell et al., 2006; Vikanes et al., 2010).

Although the reason for the reduced risk of HG associated with smoking is not known, there is evidence of a damaging effect of tobacco on the placenta which could affect hormonal levels and play a role in HG: reduced placental weight (Larsen et al., 2018), decreased blood flow in the placenta (Pintican et al., 2019) and lower blood serum hCG concentrations (Korevaar et al., 2015) have been observed in pregnancies involving smoking. In contrast, in pregnancies with HG, placental weight has been found to be higher compared to pregnancies without HG (Bolin et al., 2013; Vandraas et al., 2013), and the effect of smoking on HG may thus be mediated by impaired placental function.

6.7.2.2 Marital status

Results regarding associations between living alone and HG are summarized in **Figure 26**.

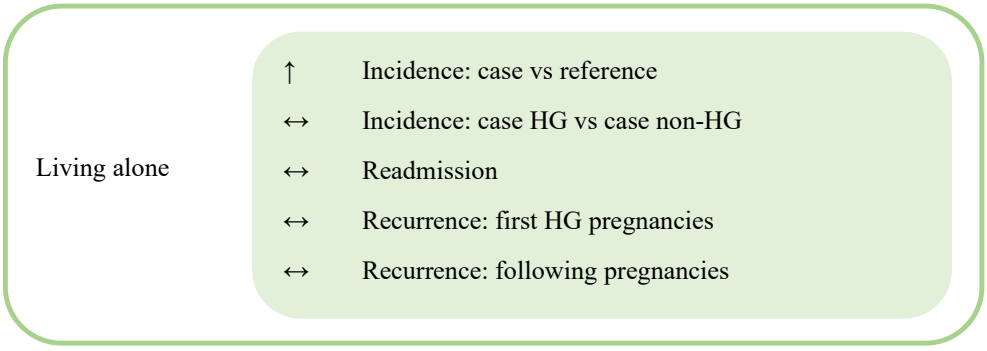

Figure 26. Association between marital status and HG. ↑ Increased odds, ↔ No association.

In general, living alone during pregnancy was relatively rare: 6.3% of women with HG and 5.5% of women without HG were living alone. When pregnancies of women with and without HG were compared, an increased risk of HG was observed among women living alone compared to women living with partner, but the difference was small, and there was no effect on readmissions or recurrence of HG.

Previous results regarding marital or cohabiting status and HG are sparse and inconclusive: in a Californian register study of 520,739 births, women diagnosed with HG were less likely to be married than women without HG diagnosis (Bailit, 2005), whereas in a Norwegian register study of 900,074 primiparous women, single and cohabiting women had a lower risk of HG than married women (Vikanes et al., 2008). Thus, the role of marital status in HG remains undefined. The small observed increased risk may reflect availability of support in daily life, disposing women living alone to be more likely to seek medical care and hence be diagnosed. Also,

hospitalization due to HG may be needed in situations where the patient could cope at home with a spouse's help but not alone. Nevertheless, women living alone may have other close connections, and being single does not exclude good social support.

6.7.2.3 Employment status

Results regarding associations between employment status and HG are recapped in **Figure 27**. In **Studies I** and **II**, the other classes were compared to the upper-level white collar group, whereas in **Study III**, the variable was dichotomised into employed and unemployed/at home, with the employed group as reference.

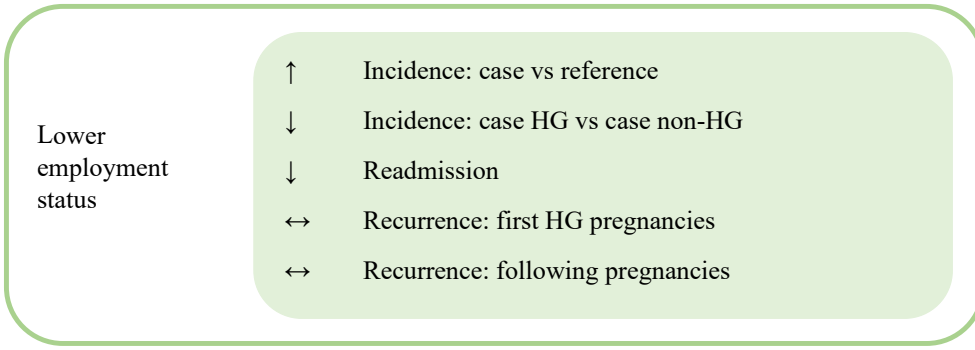

Figure 27. Association between employment status and HG. Results of univariable comparison. ↑ Increased odds, ↓ Decreased odds, ↔ No association.

In the present study, HG was least common in the highest employment status class, upper-level white collar. This is in line with earlier studies where various socioeconomically unfavourable situations have been found to be associated with elevated risk of NVP (Kramer et al., 2013; Källén et al., 2003; Markl et al., 2008) and HG (Fiaschi et al., 2016). In addition to employment, education has been used as a proxy for socioeconomic status, and women with lower education level have been found to be more likely to suffer from NVP (Munch et al., 2011; Weigel et al., 2000). Women living in areas of lowest 10th percentile of average price of housing in home address were also found to be more likely to have HG (Roseboom et al., 2011).

However, this association was not found in the other comparisons. When HG pregnancies of women with HG were compared to their non-HG pregnancies, HG was least common in pregnancies where the mother was at home (for instance, housewife or unemployed). This may in some instances reflect the need of being diagnosed and treated while working: an employee often needs a medical sick leave attestation as soon as her symptoms prevent her from working, whereas if no attestation is needed, the pregnant woman may be able to rest at home and only be diagnosed when she can no longer cope without medical care. Changes in women's

employment situation from one pregnancy to another could also play a role. In our study, readmissions due to HG were least likely in lower-level white collar and blue collar occupation groups, whereas in a previous study, low socioeconomic status has been found to be associated with higher risk of readmission (Fiaschi et al., 2016). Employment status and recurrence of HG did not show any association.

Socioeconomic differences in Finland are in general relatively small, with taxes and transfers further reducing eventual inequalities (Department of Economic and Social Affairs of the United Nations, 2020). In addition, the high number of missing data in this variable in our data set indicates that these results should be interpreted with caution and further research focusing on socioeconomic factors in more detail will be needed to elucidate these questions.

6.7.2.4 Municipality population

Summary of the results about municipality population and HG are presented in **Figure 28**. Population count of <10,000 inhabitants was used as reference.

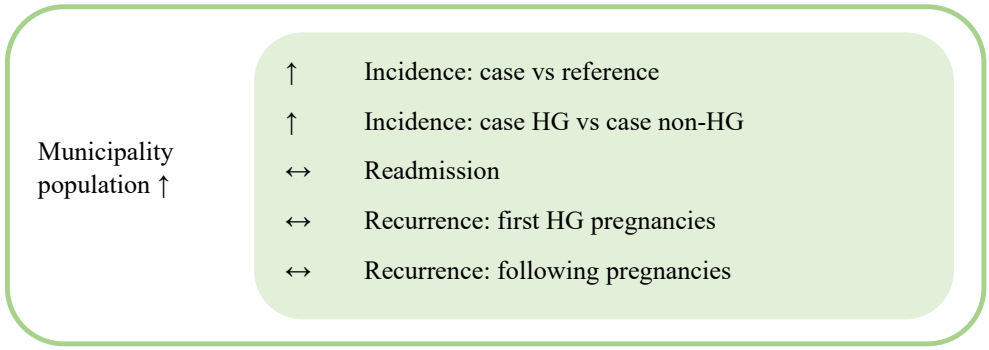

Figure 28. Association between higher municipality population and HG. ↑ Increased odds, ↔ No association.

In comparisons of pregnancies of women with and without HG, as well as in comparison to non-HG pregnancies of women with HG, municipality population was associated with HG: women in municipalities with more than 100,000 inhabitants were more likely to be diagnosed with HG than women living in municipalities with fewer than 10,000 inhabitants. One possible explanation for the differences may be better availability of care in the larger municipalities compared to smaller ones; although the Finnish health care system statutorily guarantees equal access to health care for every citizen, including referral from primary care to specialized care, long distances to nearest health care units in small rural communities may raise the threshold for seeking medical care with milder

symptoms. Another factor to consider are social support networks. Living in smaller communities closer to their relatives may allow women to cope at home longer, thus reducing the need of medical interventions, whereas women who have moved to bigger cities may have more limited support networks. Proximity to the nearest health care unit may in turn lower the threshold for seeking medical care.

Previous results regarding HG in different areas are sparse. In one Dutch study (Roseboom et al., 2011), degree of urbanization was studied and found not to be associated with HG. The variable was based on the number of addresses per square kilometre and categorised as very urban (≥2,500 addresses/km^2), intermediate urban/rural (between 500 and 2,500 addresses/km^2) and very rural (<500 addresses/km^2). However, compared to Finland, the population density in the Netherlands is much higher: only 1% of Finnish municipalities have more than 500 addresses/km^2 and there are none with more than 2,500 addresses/km^2. Thus, 99% of Finnish municipalities, including most of the biggest cities, would be categorized as very rural according to these criteria. Most of the Dutch population lives as near to their closest health care unit as people in the largest cities in Finland, and these results cannot therefore directly be compared.

6.7.3 Pregnancy-related factors

Pregnancy-related factors available in the data set were ART, number of fetuses and sex of the fetus/fetuses.

6.7.3.1 ART

The results regarding associations between ART and HG are compiled in **Figure 29**. ART was dichotomized into "yes" (all ART methods) or "no", with "no" as the reference in all comparisons.

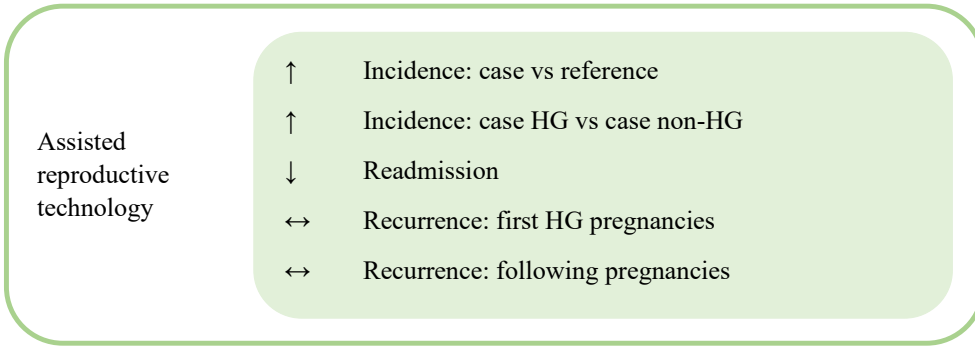

Figure 29. Association between ART and HG. ↑ Increased odds, ↓ Decreased odds, ↔ No association.

In pregnancies conceived by ART, HG was approximately 40% more common than in spontaneously conceived pregnancies. A similar increased risk has been observed earlier in a Dutch study of 1,199,218 singleton deliveries (Roseboom et al., 2011), but in an Italian study of 1,097 twin pregnancies (450 ART and 647 spontaneous), there was no difference in HG risk between pregnancies conceived by ARTs and pregnancies conceived spontaneously (Bordi et al., 2017). Different ARTs may be associated with different symptoms; in the Italian study mentioned above, in vitro fertilization was associated with higher risk of HG than ovulation induction (Bordi et al., 2017). Due to the relatively small total number of ARTs in the present study population, stratification by different ART methods was not feasible and a larger sample size would be needed to detect eventual differences between the methods in the Finnish population. The increased risk of HG in association with ARTs may be mediated by hormonal factors. Firstly, most ARTs involve hormonal treatments which may cause symptoms of HG in some women. On the other hand, the woman's own hormonal status may be altered, predisposing her to both fertility problems and HG.

Contrary to general risk of HG, ARTs were associated with lower risk of readmissions due to HG, suggesting that although ARTs may increase the likelihood of HG as such, the symptoms may not be likely to persist very long or cause need of repeated medical care.

6.7.3.2 Number of fetuses

The results regarding associations between multiple gestation and HG are summarized in **Figure 30**. Singleton pregnancies were used as reference in the comparisons.

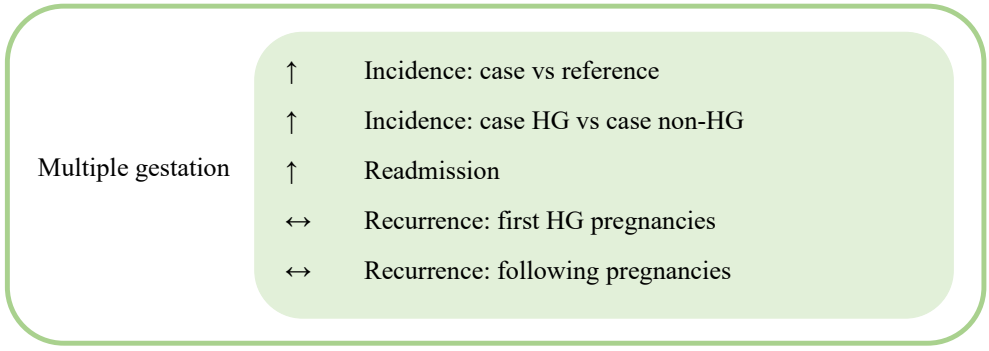

Figure 30. Association between multiple gestation and HG. ↑ Increased odds, ↔ No association.

Multiple gestation was associated with increased risk of HG in comparisons of HG pregnancies of women with and without HG and non-HG pregnancies of women with HG, as well as in pregnancies with readmission due to HG. This association has been fairly well established in earlier studies both in the context of HG (Bailit, 2005; Basso et al., 2001; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987; Morgan et al., 2017; Vikanes et al., 2008) and readmissions due to HG (Fiaschi et al., 2016).

The physiologic mechanism by which multiple gestation may affect HG is not known, but the observed higher maternal serum concentration of hCG in multiple pregnancies suggest that hCG may be a mediating factor in the process (Eskild et al., 2012; Morgan et al., 2017; Verberg et al., 2005).

Multiple gestation was not associated with recurrence risk of HG, although multiple gestation was somewhat more frequent in pregnancies with recurring HG compared to pregnancies without recurring HG, but there were only few occurrences of multiple gestation in each group and the difference was not statistically significant.

6.7.3.3 Sex of the fetus

Summary of the results about sex of the fetus and HG are presented in **Figure 31**. Male sex was used as the reference class in the comparisons.

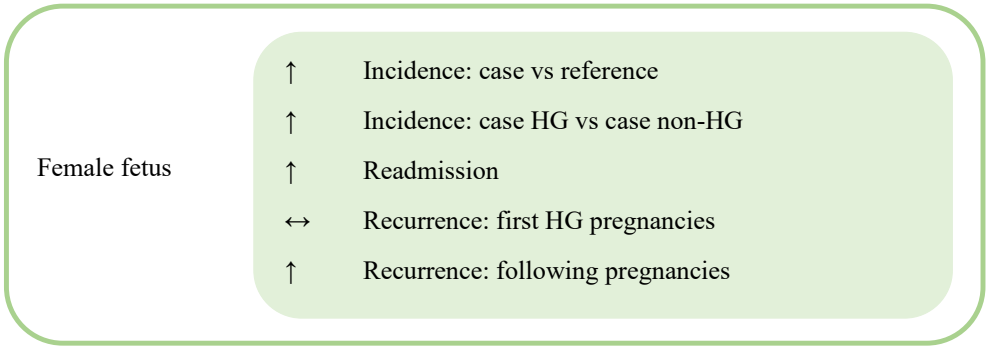

Figure 31. Association between female fetus and HG. ↑ Increased odds, ↔ No association

In all comparisons where HG pregnancies were compared to non-HG pregnancies, female fetus was associated with higher risk of HG. In addition, female fetus was associated with increased risk of readmission due to HG, indicating a possible effect on symptom severity or duration. As expected, female fetus in first HG pregnancy did not have any effect on recurrence of HG in following pregnancies.

These results are unanimous with previous results about sex of the fetus and HG: in pregnancies with HG, female fetuses have been observed to be more common than

male (Basso et al., 2001; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987; Peled et al., 2013; Roseboom et al., 2011), and risk of readmission due to HG has also been found to be higher in association with female fetus (Fiaschi et al., 2016).

Thus, the association of female fetus with elevated risk of HG can be considered to be quite well confirmed, although the physiologic mechanism causing it are not known. Hypotheses of hormonal action specific to or more pronounced with female fetus have been proposed based on the observed higher maternal serum hCG (Deruelle et al., 2002; Korevaar et al., 2015; Peled et al., 2013) and estrogen concentrations (Fiaschi et al., 2016) with female fetus. However, as HG symptoms usually begin early in the pregnancy, more specific data regarding the timing of altered hormonal levels associated with female fetus are needed to determine the possible mechanism of action. Also, as all pregnancies with female fetus certainly do not involve HG symptoms, these factors are likely to be connected to individual maternal susceptibilities thus far unknown.

6.8 Clinical implications

The observed incidence of HG in Finland, 1.3%, or approximately one in every 75 pregnancies, equals approximately 650 HG pregnancies in Finland each year. This poses a dual challenge to the health care system: on one hand, there are hundreds of women with HG in need of treatment at any given moment, but on the other hand, in areas with a low population count or a low number of deliveries, health care personnel may encounter HG patients very rarely. In consequence, even professionals involved in caring for pregnant women may not be familiar with HG, limiting their preparedness to identify the condition and treat it efficiently. One of the obstacles may be the high prevalence of NVP – compared to HG, NVP is so much more common that the occasional HG cases may remain unnoticed or considered as normal pregnancy symptoms, delaying access to more effective treatment options, and hence causing the vexation and despair often described by women with HG.

In the present study, readmissions due to HG were more common than was known earlier, and it was not rare for outpatient visits or hospitalizations due to HG to occur after the first trimester. Therefore, planning for long-term treatment of HG is highly important to avoid frustration ensuing from ungrounded hope of quick recovery.

Predicting recurrence of HG in following pregnancies would be desirable but it has turned out to be difficult. On the positive side, in the present study, HG was diagnosed only in one of every four or five pregnancies after an initial HG pregnancy, and being diagnosed with HG in all pregnancies was rare, only about 5%. However, the results only represent diagnosed cases, and a pregnancy without HG

diagnosis does not necessarily mean a symptom-free pregnancy. Predicting recurrence of HG based on maternal, environmental, or pregnancy-related factors in the first HG pregnancy was not feasible, and it would thus be recommendable to prepare for eventual recurrence with planning ahead for close follow-up in early pregnancy and timely treatment of symptoms as soon as they arise. Low-threshold access to treatment should be assured in the health care system to make sure women with HG receive adequate care. Early management of symptoms has been shown to prevent aggravation of the condition and may hence prevent the most severe forms of NVP and HG (Dean, 2014; Koren et al., 2004). Having a predefined process for such purposes in the health care system would be valuable.

The results regarding pregnancy terminations call for attention. Earlier, smaller studies have indicated that even planned pregnancies have been terminated due to HG (Havnen et al., 2019), and in the present study, a higher frequency of pregnancy terminations among women with HG compared to women without HG was found on the population level. This signifies a substantial degree of personal affliction in the families weighing the decision to carry on or to terminate a desired pregnancy which has become too devastating for the expecting mother. Especially in situations where thoughts of pregnancy termination arise due to unbearable HG symptoms in a wanted pregnancy, the importance of adequate treatment cannot be emphasized too much.

6.9 Future aspects

As knowledge about HG accrues, the mechanisms of action of the risk factors will be better understood, and eventually more treatment options will become available for the patients.

Since several aspects of HG still remain undetermined, it will be beneficial to prioritize the most relevant research topics. For this purpose, a patient–clinician James Lind Alliance partnership has been established (Dean et al., 2021), and in their first report, the top four questions selected as most pertinent by patients and other stakeholders were: *Can we find a cure? How can we most effectively manage HG? What causes HG? Is HG preventable?* These extensive questions cannot be quickly replied with one or a few studies, highlighting the importance of coordinated long-term research efforts. To reach such ambitious goals, specific study designs appropriate for each research question will be needed. For instance, to study recurrence or prevention of HG in following pregnancies, prospective cohort studies with recruitment after the first HG pregnancy and long-term follow-up would be ideal, whereas for studying effectiveness of specific treatment options, randomized controlled trial is the most reliable study structure. Due to the relative rarity of HG, multicentre studies would be needed to ensure efficient recruitment of sufficient numbers of women in reasonable time. Advances in genetic research will elucidate

the possible hereditarity of HG, hopefully leading to discoveries regarding novel treatment options.

From the patients' perspective, timely access to medical care is crucial, and this issue could be addressed by focusing on removal of barriers impeding recognition of HG. Reliable measuring tools for assessing severity of symptoms to differentiate HG from the milder NVP could be one solution for this issue. One of the most effortless tools, the PUQE questionnaire, consists of three questions and could be easily applied in health care. Using such a tool would enable health care personnel in local health care clinics, occupational health care and emergency departments to quickly recognize patients needing expeditious care, and this will be one of the focal points for our research group in the future.

7 Conclusions

In the present thesis, HG was studied from different points of view using Finnish health care register data for measuring the incidence, readmissions, and recurrence rate of HG, as well as associations between several maternal, environmental, and pregnancy-related factors in these settings. Furthermore, associations between HG and the number of deliveries, pregnancy terminations, and sterilizations were evaluated.

The main conclusions were:

1. The incidence of HG in Finland was 1.3%, equalling approximately 650 HG pregnancies annually. Pregnancy-related factors such as ART, multiple gestation, and female sex of the fetus were associated with elevated risk of HG, and smoking was associated with lower risk, whereas the association of other factors with HG depended on the comparison settings.
2. HG caused approximately 1,300 outpatient visits and 700 hospitalizations/ year, with a clear increase in outpatient care and decrease of hospitalizations. Readmissions due to HG occurred in 61% of pregnancies with HG, and the need of medical care was not limited to the first trimester of pregnancy, underscoring the importance of preparing for eventual long-term treatment of HG. Symptoms persisting longer than expected may cause discouragement, and realistic evaluation of duration of HG is hence valuable. However, only few factors associated with readmission due to HG were identified, and need of long-term medical care cannot thus be unambiguously predicted.
3. HG recurred in almost one fourth of pregnancies following an earlier hyperemetic pregnancy, and 5% of women who had more than two pregnancies resulting in delivery had HG in all of them. However, predicting recurrence of HG based on maternal or other factors in the first HG pregnancy was not feasible, as only few factors were associated with recurring HG. Thus, HG in a previous pregnancy can be considered a major risk factor for HG in future pregnancies, and preparation for eventual

recurrence of HG ought to be provided as routine prepregnancy planning for women who have experienced HG.

4. HG appears to affect family planning to some degree, attested by the higher number of pregnancy terminations and sterilizations among women diagnosed with HG. However, women with HG did not have fewer deliveries compared to women never diagnosed with HG, denoting that HG may not necessarily delimit the ultimate number of children a woman will have during her lifetime.

The aims of quantifying several aspects of HG; incidence, outpatient visits and hospitalizations, readmissions, and recurrence, were attained well. Questions regarding factors associated with HG were not as straightforward to elucidate; factors associated with HG were identified, but depending on the comparison settings, different factors were associated with different aspects of HG. Furthermore, as most of the observed factors such as maternal age, parity, multiple gestation, or sex of the fetus, are not influenceable, these results do not enable diminishing individual women's risk of HG, readmission risk or risk of recurrence of HG in following pregnancies.

The relative rarity of HG as opposed to common nausea and vomiting during pregnancy may have contributed to a comparative lack of knowledge about HG leading to delays in access to care, hence ensuing frustration and despair among women suffering from HG as described in earlier studies. The higher number of pregnancy terminations among women with HG observed in this study may reflect this phenomenon on the population scale. The present thesis addresses these issues by accumulating knowledge about HG to better understand the disease course and the need of care for benefiting the patients – recognizing and treating the condition appropriately and timely is instrumental for lightening the burden of illness caused by HG.

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The days are long but the years are short.

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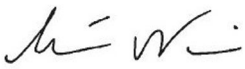

Miina Nurmi

References

Adams, M. M., Harlass, F. E., Sarno, A. P., Read, J. A., & Rawlings, J. S. 1994. Antenatal hospitalization among enlisted servicewomen, 1987-1990. *Obstetrics and Gynecology*, 84 (1), 35-39.

Agmon, N., Sade, S., Pariente, G., Rotem, R., & Weintraub, A. Y. 2019. Hyperemesis gravidarum and adverse pregnancy outcomes. *Archives of Gynecology and Obstetrics*, 300 (2), 347-353.

Aitokallio-Tallberg, A., & Pakarinen, P. 2005. Voimakas raskaudenaikainen pahoinvointi. *Duodecim; Lääketieteellinen Aikakauskirja*, 121 (13), 1435-1440.

Aka, N., Atalay, S., Sayharman, S., Kilic, D., Kose, G., & Kucukozkan, T. 2006. Leptin and leptin receptor levels in pregnant women with hyperemesis gravidarum. *The Australian & New Zealand Journal of Obstetrics & Gynaecology*, 46 (4), 274-277.

Albayrak, M., Karatas, A., Demiraran, Y., Erman, H., Topuz, S., Biyik, I., Uzun, H., & Erkan, M. 2013. Ghrelin, acylated ghrelin, leptin and PYY-3 levels in hyperemesis gravidarum. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 26 (9), 866-870.

Al-Yatama, M., Diejomaoh, M., Nandakumaran, M., Monem, R. A., Omu, A. E., & Al Kandari, F. 2002. Hormone profile of Kuwaiti women with hyperemesis gravidarum. *Archives of Gynecology and Obstetrics*, 266 (4), 218-222.

American College of Obstetrics and Gynecology. 2018. ACOG practice bulletin 189: Nausea and vomiting of pregnancy. *Obstetrics and Gynecology*, 131 (5), 935.

American College of Obstetrics and Gynecology. 2019. ACOG practice bulletin no. 208: Benefits and risks of sterilization. *Obstetrics and Gynecology*, 133 (3), e194-e207.

Anderka, M., Mitchell, A. A., Louik, C., Werler, M. M., Hernández-Diaz, S., & Rasmussen, S. A. 2012. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, 94 (1), 22-30.

Arslan, E. O., Cengiz, L., & Arslan, M. 2003. Thyroid function in hyperemesis gravidarum and correlation with serum leptin levels. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 83 (2), 187-188.

Assadi, A., Zahabi, A., & Hart, R. A. 2020. GDF15, an update of the physiological and pathological roles it plays: A review. *Pflugers Archiv : European Journal of Physiology*, 472 (11), 1535-1546.

Attard, C. L., Kohli, M. A., Coleman, S., Bradley, C., Hux, M., Atanackovic, G., & Torrance, G. W. 2002. The burden of illness of severe nausea and vomiting of pregnancy in the United States. *American Journal of Obstetrics and Gynecology*, 186 (5 Suppl Understanding), S220-7.

Aydın, M., Tolunay, H. E., Varlı, E. N., Boza, B., Şahin, Ö., Özer, S., & Dülger, A. C. 2020. Helicobacter pylori infection in amniotic fluid may cause hyperemesis gravidarum. *The Yale Journal of Biology and Medicine*, 93 (4), 487-493.

Ayyavoo, A., Derraik, J. G., Hofman, P. L., Biggs, J., Bloomfield, F. H., Cormack, B. E., Stone, P., & Cutfield, W. S. 2013. Severe hyperemesis gravidarum is associated with reduced insulin sensitivity in the offspring in childhood. *The Journal of Clinical Endocrinology and Metabolism*, 98 (8), 3263-3268.

Baba, Y., Morisawa, H., Saito, K., Takahashi, H., Rifu, K., & Matsubara, S. 2016. Intraperitoneal hemorrhage in a pregnant woman with hyperemesis gravidarum: Vitamin K deficiency as a possible cause. *Case Reports in Obstetrics and Gynecology*, 2016, 5384943.

Bacak, S. J., Callaghan, W. M., Dietz, P. M., & Crouse, C. 2005. Pregnancy-associated hospitalizations in the United States, 1999-2000. *American Journal of Obstetrics and Gynecology*, 192 (2), 592-597.

Bacq, Y. 2011. Liver diseases unique to pregnancy: A 2010 update. *Clinics and Research in Hepatology and Gastroenterology*, 35 (3), 182-193.

Bailit, J. L. 2005. Hyperemesis gravidarum: Epidemiologic findings from a large cohort. *American Journal of Obstetrics and Gynecology*, 193 (3 Pt 1), 811-814.

Balci, S., Tohma, Y. A., Esin, S., Onalan, G., Tekindal, M. A., & Zeyneloglu, H. B. 2020. Gut dysbiosis may be associated with hyperemesis gravidarum. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, Epub, <https://doi.org/10.1080/14767058.2020.1777268>.

Banskota, S., Ghia, J. E., & Khan, W. I. 2019. Serotonin in the gut: Blessing or a curse. *Biochimie*, 161, 56-64.

Bashiri, A., Neumann, L., Maymon, E., & Katz, M. 1995. Hyperemesis gravidarum: Epidemiologic features, complications and outcome. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 63 (2), 135-138.

Basso, O., & Olsen, J. 2001. Sex ratio and twinning in women with hyperemesis or pre-eclampsia. *Epidemiology*, 12 (6), 747-749.

Bennett, T. A., Kotelchuck, M., Cox, C. E., Tucker, M. J., & Nadeau, D. A. 1998. Pregnancy-associated hospitalizations in the United States in 1991 and 1992: A comprehensive view of maternal morbidity. *American Journal of Obstetrics and Gynecology*, 178 (2), 346-354.

Beyazit, F., Turkon, H., Pek, E., Ozturk, F. H., & Unsal, M. 2018. Elevated circulating nitric oxide levels correlates with enhanced oxidative stress in patients with hyperemesis gravidarum. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 38 (5), 668-673.

Bhanja, D. B., Mondal, S., Sil, A., Das, A., Panigrahi, A., & Biswas, S. K. 2021. Post-emesis periorbital purpura in hyperemesis gravidarum. *International Journal of Dermatology*, 60 (3), e117-e119.

Blankenstein, T. J., Kainer, F., Friese, K., & Mylonas, I. 2009. Extended hyperemesis gravidarum in a patient after total thyroidectomy. *Archives of Gynecology and Obstetrics*, 280 (6), 1029-1031.

Boateng, A. A., Sriram, K., Meguid, M. M., & Crook, M. 2010. Refeeding syndrome: Treatment considerations based on collective analysis of literature case reports. *Nutrition*, 26 (2), 156-167.

Body, C., & Christie, J. A. 2016. Gastrointestinal diseases in pregnancy: Nausea, vomiting, hyperemesis gravidarum, gastroesophageal reflux disease, constipation, and diarrhea. *Gastroenterology Clinics of North America*, 45 (2), 267-283.

Boelig, R. C., Barton, S. J., Saccone, G., Kelly, A. J., Edwards, S. J., & Berghella, V. 2018. Interventions for treating hyperemesis gravidarum: A Cochrane systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 31 (18), 2492-2505.

Bolin, M., Akerud, H., Cnattingius, S., Stephansson, O., & Wikstrom, A. K. 2013. Hyperemesis gravidarum and risks of placental dysfunction disorders: A population-based cohort study. *BJOG : An International Journal of Obstetrics and Gynaecology*, 120 (5), 541-547.

Boneva, R. S., Moore, C. A., Botto, L., Wong, L. Y., & Erickson, J. D. 1999. Nausea during pregnancy and congenital heart defects: A population-based case-control study. *American Journal of Epidemiology*, 149 (8), 717-725.

Bordi, G., D'Ambrosio, A., Gallotta, I., Di Benedetto, L., Frega, A., Torcia, F., Schimberni, M., Bonito, M., & Caserta, D. 2017. The influence of ovulation induction and assisted conception on maternal

and perinatal outcomes of twin pregnancies. *European Review for Medical and Pharmacological Sciences*, 21 (18), 3998-4006.

Bottomley, C., & Bourne, T. 2009. Management strategies for hyperemesis. *Best Practice & Research. Clinical Obstetrics & Gynaecology*, 23 (4), 549-564.

Bronshtein, M., Gover, A., Beloosesky, R., Dabaja, H., Ginsberg, Y., Weiner, Z., & Khatib, N. 2018. Characteristics and outcomes of ptyalism gravidarum. *The Israel Medical Association Journal : IMAJ*, 20 (9), 573-575.

Buckwalter, J. G., & Simpson, S. W. 2002. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. *American Journal of Obstetrics and Gynecology*, 186 (5 Suppl Understanding), S210-4.

Cameron, E. L. 2014. Pregnancy and olfaction: A review. *Frontiers in Psychology*, 5, 67, 1-10.

Cape, A. V., Mogensen, K. M., Robinson, M. K., & Carusi, D. A. 2014. Peripherally inserted central catheter (PICC) complications during pregnancy. *JPEN. Journal of Parenteral and Enteral Nutrition*, 38 (5), 595-601.

Cedergren, M., Brynhildsen, J., Josefsson, A., Sydsjo, A., & Sydsjo, G. 2008. Hyperemesis gravidarum that requires hospitalization and the use of antiemetic drugs in relation to maternal body composition. *American Journal of Obstetrics and Gynecology*, 198 (4), 412.e1-412.e5.

Cengiz, H., Dagdeviren, H., Caypinar, S. S., Kanawati, A., Yildiz, S., & Ekin, M. 2015. Plasma serotonin levels are elevated in pregnant women with hyperemesis gravidarum. *Archives of Gynecology and Obstetrics*, 291 (6), 1271-1276.

Chen, X., Yang, X., & Cheng, W. 2012. Diaphragmatic tear in pregnancy induced by intractable vomiting: A case report and review of the literature. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 25 (9), 1822-1824.

Chin, R. K. 1989. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 33 (3), 215-219.

Chou, F. H., Lin, L. L., Cooney, A. T., Walker, L. O., & Riggs, M. W. 2003. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. *Journal of Nursing Scholarship : An Official Publication of Sigma Theta Tau International Honor Society of Nursing*, 35 (2), 119-125.

Chraibi, Z., Ouldamer, L., Body, G., & Bacq, Y. 2015. Hyperemesis gravidarum: A ten-year French retrospective study of 109 patients. *Presse Medicale*, 44 (1), e13-22.

Christodoulou-Smith, J., Gold, J. I., Romero, R., Goodwin, T. M., Macgibbon, K. W., Mullin, P. M., & Fejzo, M. S. 2011. Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 24 (11), 1307-1311.

Clark, S. M., Dutta, E., & Hankins, G. D. 2014. The outpatient management and special considerations of nausea and vomiting in pregnancy. *Seminars in Perinatology*, 38 (8), 496-502.

Cohen, J., Ducarme, G., Neuman, D., & Uzan, M. 2007. Approche psychosomatique des vomissements incoercibles du premier trimestre. *Gynécologie Obstétrique & Fertilité*, 35 (6), 565-569.

Cole, L. A. 2010. Biological functions of hCG and hCG-related molecules. *Reproductive Biology and Endocrinology : RB&E*, 8, 102, 1-14.

Colodro-Conde, L., Jern, P., Johansson, A., Sánchez-Romera, J. F., Lind, P. A., Painter, J. N., Ordoñana, J. R., & Medland, S. E. 2016. *Nausea and vomiting during pregnancy is highly heritable. Behavior Genetics*, 46 (4), 481-491.

Conchillo, J. M., & Koek, G. H. 2002. Hyperemesis gravidarum and severe liver enzyme elevation. *Journal of Hepatology*, 37 (1), 162-163.

Czeizel, A. E., & Puho, E. 2004. Association between severe nausea and vomiting in pregnancy and lower rate of preterm births. *Paediatric and Perinatal Epidemiology*, 18 (4), 253-259.

Czeizel, A. E., Puho, E., Acs, N., & Banhidy, F. 2006. Inverse association between severe nausea and vomiting in pregnancy and some congenital abnormalities. *American Journal of Medical Genetics. Part A*, 140 (5), 453-462.

Czeizel, A. E., Sarkozi, A., & Wyszynski, D. F. 2003. Protective effect of hyperemesis gravidarum for nonsyndromic oral clefts. *Obstetrics and Gynecology*, 101 (4), 737-744.

Das, K. 1898. Obstetrics, gynaecology, and paediatrics: - hyperemesis gravidarum. *The Indian Medical Gazette*, 33 (2), 70-72.

David, M., Borde, T., & Siedentopf, F. 2012. Do immigration and acculturation have an impact on hyperemesis gravidarum? results of a study in Berlin/Germany. *Journal of Psychosomatic Obstetrics and Gynaecology*, 33 (2), 78-84.

Dean, C. R. 2014. Helping women prepare for hyperemesis gravidarum. *British Journal of Midwifery*, 22 (12), 847-852.

Dean, C. R., Bierma, H., Clarke, R., Cleary, B., Ellis, P., Gadsby, R., Gauw, N., Lodge, K., MacGibbon, K., McBride, M., Munro, D., Nelson-Piercy, C., O'Hara, M., Penny, H., Shorter, K., Spijker, R., Trovik, J., Watford, E., & Painter, R. C. 2021. A patient-clinician James Lind alliance partnership to identify research priorities for hyperemesis gravidarum. *BMJ Open*, 11 (1), e041254-2020-041254.

Dean, C. R., Bruin, C. M., O'Hara, M. E., Roseboom, T. J., Leeflang, M. M., Spijker, R., & Painter, R. C. 2019. The chance of recurrence of hyperemesis gravidarum: A systematic review. *European Journal of Obstetrics & Gynecology and Reproductive Biology*: X, 5, 100105.

Demir, B., Erel, C. T., Haberal, A., Ozturk, N., Guler, D., & Kocak, M. 2006. Adjusted leptin level (ALL) is a predictor for hyperemesis gravidarum. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 124 (2), 193-196.

Department of Economic and Social Affairs of the United Nations. (2020). Inequality in a rapidly changing world. <https://www.un.org/development/desa/dspd/wp-content/uploads/sites/22/2020/01/World-Social-Report-2020-FullReport.pdf> Date of access: May 4, 2021.

Depue, R. H., Bernstein, L., Ross, R. K., Judd, H. L., & Henderson, B. E. 1987. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: A seroepidemiologic study. *American Journal of Obstetrics and Gynecology*, 156 (5), 1137-1141.

Derbent, A. U., Yanik, F. F., Simavli, S., Atasoy, L., Urun, E., Kuscu, U. E., & Turhan, N. O. 2011. First trimester maternal serum PAPP-A and free beta-HCG levels in hyperemesis gravidarum. *Prenatal Diagnosis*, 31 (5), 450-453.

Deruelle, P., Dufour, P., Subtil, D., Houfflin-Debarge, V., Dherbomez, A., Wemeau, J. L., & Puech, F. 2002. Vomissements incoercibles du premier trimestre de la grossesse : Rôle de l'hyperthyroïdie biologique et du sexe fœtal. *Gynécologie Obstétrique & Fertilité*, 30 (3), 204-209.

Devignes, J., Grare, M., Raft, J., Vial, F., Hacquard, M., Bouaziz, H., Lecompte, T., & de Maistre, E. 2009. A case of cutaneous and mucous haemorrhage secondary to vitamin K deficiency in hyperemesis gravidarum. *Annales Françaises d'Anesthésie Et De Réanimation*, 28 (7-8), 697-700.

Dodds, L., Fell, D. B., Joseph, K. S., Allen, V. M., & Butler, B. 2006. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstetrics and Gynecology*, 107 (2 Pt 1), 285-292.

D'Orazio, L. M., Meyerowitz, B. E., Korst, L. M., Romero, R., & Goodwin, T. M. 2011. Evidence against a link between hyperemesis gravidarum and personality characteristics from an ethnically diverse sample of pregnant women: A pilot study. *Journal of Women's Health* (2002), 20 (1), 137-144.

Duman, N. B., Ozcan, O., & Bostanci, M. O. 2015. Hyperemesis gravidarum affects maternal sanity, thyroid hormones and fetal health: A prospective case control study. *Archives of Gynecology and Obstetrics*, 292 (2), 307-312.

Dypvik, J., Pereira, A. L., Tanbo, T. G., & Eskild, A. 2018. Maternal human chorionic gonadotrophin concentrations in very early pregnancy and risk of hyperemesis gravidarum: A retrospective cohort

study of 4372 pregnancies after in vitro fertilization. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 221, 12-16.

Ebrahimi, N., Maltepe, C., Bournissen, F. G., & Koren, G. 2009. Nausea and vomiting of pregnancy: Using the 24-hour pregnancy-unique quantification of emesis (PUQE-24) scale. *Journal of Obstetrics and Gynaecology Canada*, 31 (9), 803-807.

Ege, S., Kolusari, A., Bugdayci, G., Cim, N., Bademkıran, M. H., Peker, N., Erdem, S., Özgökçe, C., & Yıldızhan, R. 2019. Ghrelin does not change in hyperemesis gravidarum. *Ginekologia Polska*, 90 (12), 699-701.

Ege, S., Peker, N., Bademkıran, M. H., Köçeroğlu, R., Erel, Ö., Erdem, S., Özgökçe, Ç., & Yıldızhan, R. 2020. The thiol/disulfide balance in ketone positive and ketone negative pregnant women with nausea and vomiting - a prospective study in a tertiary center. Ginekologia Polska, 91 (4), 207-209.

Ellilä, P., Laitinen, L., Nurmi, M., Rautava, P., Koivisto, M., & Polo-Kantola, P. 2018. Nausea and vomiting of pregnancy: A study with pregnancy-unique quantification of emesis questionnaire. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 230, 60-67.

Engin-Ustun, Y., Tonguç, E., Var, T., Deveer, R., Yilmaz, N., Danisman, N., Besli, M., & Mollamahmutoglu, L. 2013. Vaspin and C-reactive protein levels in hyperemesis gravidarum. *European Review for Medical and Pharmacological Sciences*, 17 (1), 138-140.

Ensiyeh, J., & Sakineh, M. A. 2009. Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: A randomised controlled trial. *Midwifery*, 25 (6), 649-653.

Erick, M. 2014. Hyperemesis gravidarum: A case of starvation and altered sensorium gestosis (ASG). *Medical Hypotheses*, 82 (5), 572-580.

Erlandsson, G., Lambe, M., Cnattingius, S., & Ekbom, A. 2002. Hyperemesis gravidarum and subsequent breast cancer risk. *British Journal of Cancer*, 87 (9), 974-976.

Eskild, A., Fedorcsak, P., Mørkrid, L., & Tanbo, T. G. 2012. Maternal body mass index and serum concentrations of human chorionic gonadotropin in very early pregnancy. *Fertility and Sterility*, 98 (4), 905-910.

Fairweather, D. V. 1968. Nausea and vomiting in pregnancy. *American Journal of Obstetrics and Gynecology*, 102 (1), 135-175.

Farbu, J., Haugen, M., Meltzer, H. M., & Brantsæter, A. L. 2014. Impact of singlehood during pregnancy on dietary intake and birth outcomes- a study in the Norwegian mother and child cohort study. *BMC Pregnancy and Childbirth*, 14, 396-014-0396-9.

Fejzo, M. S. 2017. Measures of depression and anxiety in women with hyperemesis gravidarum are flawed. *Evidence-Based Nursing*, 20 (3), 78-79.

Fejzo, M. S. 2020. A core outcome set for hyperemesis gravidarum studies is a small step in the right direction. *BJOG : An International Journal of Obstetrics and Gynaecology*, 127 (8), 993.

Fejzo, M. S., Ching, C., Schoenberg, F. P., Macgibbon, K., Romero, R., Goodwin, T. M., & Mullin, P. M. 2012. Change in paternity and recurrence of hyperemesis gravidarum. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 25 (8), 1241-1245.

Fejzo, M. S., Fasching, P. A., Schneider, M. O., Schwitulla, J., Beckmann, M. W., Schwenke, E., MacGibbon, K. W., & Mullin, P. M. 2019. Analysis of GDF15 and IGFBP7 in hyperemesis gravidarum support causality. *Geburtshilfe Und Frauenheilkunde*, 79 (4), 382-388.

Fejzo, M. S., Ingles, S. A., Wilson, M., Wang, W., MacGibbon, K., Romero, R., & Goodwin, T. M. 2008. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 141 (1), 13-17.

Fejzo, M. S., Macgibbon, K. W., Romero, R., Goodwin, T. M., & Mullin, P. M. 2011. Recurrence risk of hyperemesis gravidarum. *Journal of Midwifery & Women's Health*, 56 (2), 132-136.

Fejzo, M. S., Magtira, A., Schoenberg, F. P., MacGibbon, K., Mullin, P., Romero, R., & Tabsh, K. 2013. Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 170 (1), 71-76.

Fejzo, M. S., Myhre, R., Colodro-Conde, L., MacGibbon, K. W., Sinsheimer, J. S., Reddy, M. V., Pajukanta, P., Nyholt, D. R., Wright, M. J., Martin, N. G., Engel, S. M., Medland, S. E., Magnus, P., & Mullin, P. M. 2017. Genetic analysis of hyperemesis gravidarum reveals association with intracellular calcium release channel (RYR2). *Molecular and Cellular Endocrinology*, 439, 308-316.

Fejzo, M. S., Poursharif, B., Korst, L. M., Munch, S., MacGibbon, K. W., Romero, R., & Goodwin, T. M. 2009. Symptoms and pregnancy outcomes associated with extreme weight loss among women with hyperemesis gravidarum. *Journal of Women's Health*, 18 (12), 1981-1987.

Fejzo, M. S., Romero, R., & Goodwin, T. M. 2010. Patients with a history of hyperemesis gravidarum have similar symptoms during egg stimulation and develop ovarian hyperstimulation syndrome: Case series. *Fertility and Sterility*, 93 (1), 267.e9-267.11.

Fejzo, M. S., Sazonova, O. V., Sathirapongsasuti, J. F., Hallgrimsdottir, I. B., Vacic, V., MacGibbon, K. W., Schoenberg, F. P., Mancuso, N., Slamon, D. J., Mullin, P. M., & 23andMe Research Team. 2018. Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. *Nature Communications*, 9 (1), 1178-018-03258-0.

Fejzo, M. S., Trovik, J., Grooten, I. J., Sridharan, K., Roseboom, T. J., Vikanes, A., Painter, R. C., & Mullin, P. M. 2019. Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nature Reviews. Disease Primers*, 5 (1), 62-019-0110-3.

Fejzo, M. S., Magtira, A., Schoenberg, F. P., Macgibbon, K., & Mullin, P. M. 2015. Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 189, 79-84.

Fell, D. B., Dodds, L., Joseph, K. S., Allen, V. M., & Butler, B. 2006. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. *Obstetrics and Gynecology*, 107 (2 Pt 1), 277-284.

Fiaschi, L., Housley, G., Nelson-Piercy, C., Gibson, J., Raji, A., Deb, S., & Tata, L. J. 2019. Assessment of discharge treatment prescribed to women admitted to hospital for hyperemesis gravidarum. *International Journal of Clinical Practice*, 73 (1), e13261.

Fiaschi, L., Nelson-Piercy, C., Deb, S., King, R., & Tata, L. J. 2019. Clinical management of nausea and vomiting in pregnancy and hyperemesis gravidarum across primary and secondary care: A population-based study. *BJOG : An International Journal of Obstetrics and Gynaecology*, 126, 1201-1211.

Fiaschi, L., Nelson-Piercy, C., Gibson, J., Szatkowski, L., & Tata, L. J. 2018. Adverse maternal and birth outcomes in women admitted to hospital for hyperemesis gravidarum: A population-based cohort study. *Paediatric and Perinatal Epidemiology*, 32 (1), 40-51.

Fiaschi, L., Nelson-Piercy, C., & Tata, L. J. 2016. Hospital admission for hyperemesis gravidarum: A nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies. *Human Reproduction*, 31 (8), 1675-1684.

Finlex. (1970a). Finnish legislation on induced abortions. <https://www.finlex.fi/fi/laki/ajantasa/1970/19700239> Date of access: October 27, 2020.

Finlex. (1970b). Finnish legislation on sterilizations. <https://www.finlex.fi/fi/laki/ajantasa/1970/19700283> Date of access: October 27, 2020.

Finnish Institute for Health and Welfare. (2020a). Care register for health care. <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care#right> Date of access: June 29, 2020.

Finnish Institute for Health and Welfare. (2020b). Medical birth register. <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns> Date of access: June 29, 2020.

Finnish Institute for Health and Welfare. (2020c). Register of induced abortions. <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-induced-abortions> Date of access: June 29, 2020.

Finnish Institute for Health and Welfare. (2020d). Register of sterilisations. <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/sterilisations> Date of access: June 29, 2020.

Finnish Institute for Health and Welfare. (2020e). Sterilization statistics. <https://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/steriloinnit> Date of access: May 15, 2021.

Firoz, T., Maltepe, C., & Einarson, A. 2010. Nausea and vomiting in pregnancy is not always nausea and vomiting of pregnancy. *Journal of Obstetrics and Gynaecology Canada*, 32 (10), 970-972.

Flake, Z. A., Linn, B. S., & Hornecker, J. R. 2015. Practical selection of antiemetics in the ambulatory setting. *American Family Physician*, 91 (5), 293-296.

Flake, Z. A., Scalley, R. D., & Bailey, A. G. 2004. Practical selection of antiemetics. *American Family Physician*, 69 (5), 1169-1174.

Foley, D., Holmes, H. J., & Kauffman, R. P. 2020. Spontaneous pneumomediastinum: An unusual complication of hyperemesis gravidarum. *BMJ Case Reports*, 13 (2), e234001.

Fruitnight, J. H. (1890). Hyperemesis gravidarum as an indication for the induction of premature labor. William Wood & Company, New York Obstetrical Society.

Fuhler, G. M. 2020. The immune system and microbiome in pregnancy. *Best Practice & Research. Clinical Gastroenterology*, 44-45, 101671.

Furneaux, E. C., Langley-Evans, A. J., & Langley-Evans, S. C. 2001. Nausea and vomiting of pregnancy: Endocrine basis and contribution to pregnancy outcome. *Obstetrical & Gynecological Survey*, 56 (12), 775-782.

Gaba, N., & Gaba, S. 2020. Study of liver dysfunction in hyperemesis gravidarum. *Cureus*, 12 (6), e8709.

Gadsby, R., Barnie-Adshead, A. M., & Jagger, C. 1993. A prospective study of nausea and vomiting during pregnancy. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, 43 (371), 245-248.

Gazmararian, J. A., Petersen, R., Jamieson, D. J., Schild, L., Adams, M. M., Deshpande, A. D., & Franks, A. L. 2002. Hospitalizations during pregnancy among managed care enrollees. *Obstetrics and Gynecology*, 100 (1), 94-100.

George, L., Granath, F., Johansson, A. L., Annerén, G., & Cnattingius, S. 2006. Environmental tobacco smoke and risk of spontaneous abortion. *Epidemiology*, 17 (5), 500-505.

Gill, S. K., Maltepe, C., Mastali, K., & Koren, G. 2009. The effect of acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. *Obstetrics and Gynecology International*, 2009, 585269.

Gissler, M., Mohangoo, A. D., Blondel, B., Chalmers, J., Macfarlane, A., Gaizauskiene, A., Gatt, M., Lack, N., Sakkeus, L., Zeitlin, J., & Euro-Peristat Group. 2010. Perinatal health monitoring in Europe: Results from the EURO-PERISTAT project. *Informatics for Health & Social Care*, 35 (2), 64-79.

Godsey, R. K., & Newman, R. B. 1991. Hyperemesis gravidarum. A comparison of single and multiple admissions. *The Journal of reproductive medicine*, 36 (4), 287-290.

Golberg, D., Szilagyi, A., & Graves, L. 2007. Hyperemesis gravidarum and helicobacter pylori infection: A systematic review. *Obstetrics and Gynecology*, 110 (3), 695-703.

Goodwin, T. M. 1998. Hyperemesis gravidarum. *Clinical Obstetrics and Gynecology*, 41 (3), 597-605.

Goodwin, T. M. 2008. Hyperemesis gravidarum. *Obstetrics and Gynecology Clinics of North America*, 35 (3), 401-17, viii.

Goodwin, T. M., Montoro, M., Mestman, J. H., Pekary, A. E., & Hershman, J. M. 1992. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. *The Journal of Clinical Endocrinology and Metabolism*, 75 (5), 1333-1337.

Goodwin, T. M., Nwankwo, O. A., O'Leary, L. D., O'Leary, D., Romero, R., & Korst, L. M. 2008. The first demonstration that a subset of women with hyperemesis gravidarum has abnormalities in the vestibuloocular reflex pathway. *American Journal of Obstetrics and Gynecology*, 199 (4), 417.e1-417.e9.

Greene, N. D., & Copp, A. J. 2014. Neural tube defects. *Annual Review of Neuroscience*, 37, 221-242.

Groleau, D., Benady-Chorney, J., Panaitoiu, A., & Jimenez, V. 2019. Hyperemesis gravidarum in the context of migration: When the absence of cultural meaning gives rise to "blaming the victim". *BMC Pregnancy and Childbirth*, 19 (1), 197-019-2344-1.

Groleau, D. 2005. La détresse et l'enfantement : L'hyperemesis gravidarum revisité en contexte migratoire. *L'Évolution Psychiatrique*, 70 (3), 623-641.

Grooten, I. J., Koot, M. H., van der Post, J. A., Bais, J. M., Ris-Stalpers, C., Naaktgeboren, C., Bremer, H. A., van der Ham, D. P., Heidema, W. M., Huisjes, A., Kleiverda, G., Kuppens, S., van Laar, J. O., Langenveld, J., van der Made, F., van Pampus, M. G., Papatsonis, D., Pelinck, M. J., Pernet, P. J., van Rheenen, L., Rijnders, R. J., Scheepers, H. C., Vogelvang, T. E., Mol, B. W., Roseboom, T. J., & Painter, R. C. 2017. Early enteral tube feeding in optimizing treatment of hyperemesis gravidarum: The maternal and offspring outcomes after treatment of HyperEmesis by refeeding (MOTHER) randomized controlled trial. *The American Journal of Clinical Nutrition*, 106 (3), 812-820.

Grooten, I. J., Painter, R. C., Pontesilli, M., van der Post, J., Mol, B., van Eijsden, M., Vrijkotte, T., & Roseboom, T. J. 2015. Weight loss in pregnancy and cardiometabolic profile in childhood: Findings from a longitudinal birth cohort. *BJOG : An International Journal of Obstetrics and Gynaecology*, 122 (12), 1664-1673.

Grooten, I. J., Roseboom, T. J., & Painter, R. C. 2016. Barriers and challenges in hyperemesis gravidarum research. *Nutrition and Metabolic Insights*, 8 (Suppl 1), 33-39.

Gross, S., Librach, C., & Cecutti, A. 1989. Maternal weight loss associated with hyperemesis gravidarum: A predictor of fetal outcome. *American Journal of Obstetrics and Gynecology*, 160 (4), 906-909.

Gungor, S., Gurates, B., Aydin, S., Sahin, I., Kavak, S. B., Kumru, S., Celik, H., Aksoy, A., Yilmaz, M., Catak, Z., Citil, C., Baykus, Y., Deniz, R., Karakaya, F., & Ozdemir, N. 2013. Ghrelins, obestatin, nesfatin-1 and leptin levels in pregnant women with and without hyperemesis gravidarum. *Clinical Biochemistry*, 46 (9), 828-830.

Hallak, M., Tsalamandris, K., Dombrowski, M. P., Isada, N. B., Pryde, P. G., & Evans, M. I. 1996. Hyperemesis gravidarum. effects on fetal outcome. *The Journal of Reproductive Medicine*, 41 (11), 871-874.

Hammar, O., Veress, B., Montgomery, A., & Ohlsson, B. 2012. Expression of luteinizing hormone receptor in the gastrointestinal tract in patients with and without dysmotility. *Drug Target Insights*, 6, 13-18.

Hastoy, A., Lien Tran, P., Lakestani, O., Barau, G., Gerardin, P., & Boukerrou, M. 2015. Hyperemesis gravidarum and pregnancy outcomes. *Journal De Gynécologie, Obstétrique Et Biologie De La Reproduction*, 44 (2), 154-163.

Havnen, G. C., Truong, M. B., Do, M. H., Heitmann, K., Holst, L., & Nordeng, H. 2019. Women's perspectives on the management and consequences of hyperemesis gravidarum - a descriptive interview study. *Scandinavian Journal of Primary Health Care*, 37 (1), 30-40.

Heino, A., Niinimaki, M., Mentula, M., & Gissler, M. 2018. How reliable are health registers? Registration of induced abortions and sterilizations in Finland. *Informatics for Health and Social Care*, 43 (3), 310-319.

Heinrichs, L. 2002. Linking olfaction with nausea and vomiting of pregnancy, recurrent abortion, hyperemesis gravidarum, and migraine headache. *American Journal of Obstetrics and Gynecology*, 186 (5 Suppl Understanding), S215-9.

Heitmann, K., Nordeng, H., Havnen, G. C., Solheimsnes, A., & Holst, L. 2017. The burden of nausea and vomiting during pregnancy: Severe impacts on quality of life, daily life functioning and

willingness to become pregnant again - results from a cross-sectional study. *BMC Pregnancy and Childbirth*, 17 (1), 75.

Heitmann, K., Svendsen, H. C., Sporsheim, I. H., & Holst, L. 2016. Nausea in pregnancy: Attitudes among pregnant women and general practitioners on treatment and pregnancy care. *Scandinavian Journal of Primary Health Care*, 34 (1), 13-20.

Helseth, R., Ravlo, M., Carlsen, S. M., & Vanky, E. E. 2014. Androgens and hyperemesis gravidarum: A case-control study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 175, 167-171.

Hershman, J. M. 1999. Human chorionic gonadotropin and the thyroid: Hyperemesis gravidarum and trophoblastic tumors. *Thyroid : Official Journal of the American Thyroid Association*, 9 (7), 653-657.

Hippocrates/The Internet Classics Archive. (2009). Aphorisms by Hippocrates, written 400 B.C.E, translated by Francis Adams. <http://classics.mit.edu/Hippocrates/aphorisms.mb.txt> Date of access: May 15, 2020.

Holmgren, C., Aagaard-Tillery, K. M., Silver, R. M., Porter, T. F., & Varner, M. 2008. Hyperemesis in pregnancy: An evaluation of treatment strategies with maternal and neonatal outcomes. *American Journal of Obstetrics and Gynecology*, 198 (1), 56.e1-56.e4.

Hooi, J. K. Y., Lai, W. Y., Ng, W. K., Suen, M. M. Y., Underwood, F. E., Tanyingoh, D., Malfertheiner, P., Graham, D. Y., Wong, V. W. S., Wu, J. C. Y., Chan, F. K. L., Sung, J. J. Y., Kaplan, G. G., & Ng, S. C. 2017. Global prevalence of helicobacter pylori infection: Systematic review and meta-analysis. *Gastroenterology*, 153 (2), 420-429.

Hornby, P. J. 2001. Central neurocircuitry associated with emesis. *The American Journal of Medicine*, 111 Suppl 8A, 106S-112S.

Hou, J. L., Wan, X. R., Xiang, Y., Qi, Q. W., & Yang, X. Y. 2008. Changes of clinical features in hydatidiform mole: Analysis of 113 cases. *The Journal of Reproductive Medicine*, 53 (8), 629-633.

Hovdenak, N., & Haram, K. 2012. Influence of mineral and vitamin supplements on pregnancy outcome. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 164 (2), 127-132.

Hudon Thibeault, A. A., Sanderson, J. T., & Vaillancourt, C. 2019. Serotonin-estrogen interactions: What can we learn from pregnancy? *Biochimie*, 161, 88-108.

Humaidan, P., Nelson, S.M., Devroey, P., Coddington, C.C., Schwartz, L.B., Gordon, K., Frattarelli, J.L., Tarlatzis, B.C., Fatemi, H.M., Lutjen, P. & Stegmann, B.J., 2016. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. *Human Reproduction*, 31 (9), 1997–2004.

Jaakkola, J. J., & Gissler, M. 2004. Maternal smoking in pregnancy, fetal development, and childhood asthma. *American Journal of Public Health*, 94 (1), 136-140.

James, W. H. 2008. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. *The Journal of Endocrinology*, 198 (1), 3-15.

James, W. H. 2012. The relevance of the epidemiology of human sex ratios at birth to some medical problems. *Paediatric and Perinatal Epidemiology*, 26 (3), 181-189.

Jansen, L., Koot, M., van‘tHooft, J., Dean, C., Bossuyt, P., Ganzevoort, W., Gauw, N., Goes, B., Rodenburg, J., Roseboom, T., Painter, R. & Grooten, I. (2019). An international definition for HG. <https://static1.squarespace.com/static/5a5dd5e2d74cffb3eaffbbc9/t/5da5c290b5d951321b80c884/1571144337599/3+20191008_consensus+definition+HG_v1.1_IJG.pdf> Date of access: February 17, 2020.

Jansen, L., Koot, M. H., Van't Hooft, J., Dean, C. R., Duffy, J., Ganzevoort, W., Gauw, N., Goes, B. Y., Rodenburg, J., Roseboom, T. J., Painter, R. C., & Grooten, I. J. 2020. A core outcome set for hyperemesis gravidarum research: An international consensus study. *BJOG : An International Journal of Obstetrics and Gynaecology*, 127 (8), 983-992.

Jansen, L. A. W., Koot, M. H., van't Hooft, J., Dean, C. R., Bossuyt, P. M. M., Ganzevoort, W., Gauw, N., Van der Goes, B. Y., Rodenburg, J., Roseboom, T. J., Painter, R. C., & Grooten, I. J. 2021.

The Windsor definition for hyperemesis gravidarum: A multistakeholder international consensus definition. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 266, 15-22.

Jarnfelt-Samsioe, A., Bremme, K., & Eneroth, P. 1986. Steroid hormones in emetic and non-emetic pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 21 (2), 87-99.

Jednak, M. A., Shadigian, E. M., Kim, M. S., Woods, M. L., Hooper, F. G., Owyang, C., & Hasler, W. L. 1999. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. *The American Journal of Physiology*, 277 (4), G855-61.

Jonsdottir, S. S., Swahnberg, K., Thome, M., Oskarsson, G. K., Bara Lydsdottir, L., Olafsdottir, H., Sigurdsson, J. F., & Steingrimsdottir, T. 2020. Pregnancy complications, sick leave and service needs of women who experience perinatal distress, weak social support and dissatisfaction in their partner relationships. *Scandinavian Journal of Caring Sciences*, 34 (1), 167-180.

Jueckstock, J. K., Kaestner, R., & Mylonas, I. 2010. Managing hyperemesis gravidarum: A multimodal challenge. *BMC Medicine*, 8, 46.

Källén, B. 1987. Hyperemesis during pregnancy and delivery outcome: A registry study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 26 (4), 291-302.

Källén, B., Lundberg, G., & Aberg, A. 2003. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta Obstetricia Et Gynecologica Scandinavica*, 82 (10), 916-920.

Kamimura, K., Abe, H., Kawai, H., Kamimura, H., Kobayashi, Y., Nomoto, M., Aoyagi, Y., & Terai, S. 2015. Advances in understanding and treating liver diseases during pregnancy: A review. *World Journal of Gastroenterology*, 21 (17), 5183-5190.

Kan, E., Emektar, E., Corbacioglu, K., Safak, T., Sariaydin, T., & Cevik, Y. 2020. Evaluation of relationship between inflammatory markers and hyperemesis gravidarum in patients admitted to emergency department. *The American Journal of Emergency Medicine*, 38 (2), 292-295.

Karaca, C., Guler, N., Yazar, A., Camlica, H., Demir, K., & Yildirim, G. 2004. Is lower socio-economic status a risk factor for helicobacter pylori infection in pregnant women with hyperemesis gravidarum? *The Turkish Journal of Gastroenterology : The Official Journal of Turkish Society of Gastroenterology*, 15 (2), 86-89.

Katz, V. L., Farmer, R., York, J., & Wilson, J. D. 2000. Mycobacterium chelonae sepsis associated with long-term use of an intravenous catheter for treatment of hyperemesis gravidarum. A case report. *The Journal of Reproductive Medicine*, 45 (7), 581-584.

Kauppila, A., Huhtaniemi, I., & Ylikorkala, O. 1979. Raised serum human chorionic gonadotrophin concentrations in hyperemesis gravidarum. *British Medical Journal*, 1 (6179), 1670-1671.

Kawamura, Y., Kawamata, K., Shinya, M., Higashi, M., Niiro, M., & Douchi, T. 2008. Vitamin K deficiency in hyperemesis gravidarum as a potential cause of fetal intracranial hemorrhage and hydrocephalus. *Prenatal Diagnosis*, 28 (1), 59-61.

Keller, J., Frederking, D., Layer, P., & Medscape. 2008. The spectrum and treatment of gastrointestinal disorders during pregnancy. *Nature Clinical Practice. Gastroenterology & Hepatology*, 5 (8), 430-443.

Kelly, T., Thomsett, H., & Ajala, T. 2011. Successful outpatient management of nausea and vomiting in pregnancy. *BMJ (Clinical Research Ed.)*, 343, d4543.

Kim, H. Y., Cho, G. J., Kim, S. Y., Lee, K. M., Ahn, K. H., Han, S. W., Hong, S. C., Ryu, H. M., Oh, M. J., Kim, H. J., & Kim, S. C. 2020. Pre-pregnancy risk factors for severe hyperemesis gravidarum: Korean population based cohort study. *Life*, 11 (1), 12.

Kjeldgaard, H. K., Eberhard-Gran, M., Benth, J. S., Nordeng, H., & Vikanes, A. V. 2017. History of depression and risk of hyperemesis gravidarum: A population-based cohort study. *Archives of Women's Mental Health*, 20 (3), 397-404.

Kjeldgaard, H. K., Eberhard-Gran, M., Benth, J. S., & Vikanes, A. V. 2017. Hyperemesis gravidarum and the risk of emotional distress during and after pregnancy. *Archives of Women's Mental Health*, 20 (6), 747-756.

Kjeldgaard, H. K., Vikanes, A., Benth, J. S., Junge, C., Garthus-Niegel, S., & Eberhard-Gran, M. 2019. The association between the degree of nausea in pregnancy and subsequent posttraumatic stress. *Archives of Women's Mental Health*, 22 (4), 493-501.

Kleine, I., Da Silva, A., Ahmed, W., Forya, F., Whitten, S. M., David, A. L., & James, C. P. 2017. Hospital admission for hyperemesis gravidarum in women at increased risk of spontaneous preterm birth. *Birth*, 44 (4), 384-389.

Koch, K. L. 2002. Gastrointestinal factors in nausea and vomiting of pregnancy. *American Journal of Obstetrics and Gynecology*, 186 (5 Suppl Understanding), S198-203.

Konikoff, T., Avraham, T., Ophir, E., & Bornstein, J. 2016. Hyperemesis gravidarum in northern Israel: A retrospective epidemiological study. *Israel Journal of Health Policy Research*, 5, 39.

Koot, M. H., Boelig, R. C., Van't Hooft, J., Limpens, J., Roseboom, T. J., Painter, R. C., & Grooten, I. J. 2018. Variation in hyperemesis gravidarum definition and outcome reporting in randomised clinical trials: A systematic review. *BJOG : An International Journal of Obstetrics and Gynaecology*, 125 (12), 1514-1521.

Koot, M. H., Grooten, I. J., Sebert, S., Koiranen, M., Jarvelin, M. R., Kajantie, E., Painter, R. C., & Roseboom, T. J. 2017. Hyperemesis gravidarum and cardiometabolic risk factors in adolescents: A follow-up of the northern Finland birth cohort 1986. *BJOG : An International Journal of Obstetrics and Gynaecology*, 124 (7), 1107-1114.

Koot, M. H., Grooten, I. J., van der Post, J. A. M., Bais, J. M. J., Ris-Stalpers, C., Leeflang, M. M. G., Bremer, H. A., van der Ham, D. P., Heidema, W. M., Huisjes, A., Kleiverda, G., Kuppens, S. M., van Laar, J. O. E. H., Langenveld, J., van der Made, F., van Pampus, M. G., Papatsonis, D., Pelinck, M. J., Pernet, P. J., van Rheenen-Flach, L., Rijnders, R. J., Scheepers, H. C. J., Vogelvang, T. E., Mol, B. W., Roseboom, T. J., & Painter, R. C. 2020. Determinants of disease course and severity in hyperemesis gravidarum. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 245, 162-167.

Koren, G., Boskovic, R., Hard, M., Maltepe, C., Navioz, Y., & Einarson, A. 2002. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *American Journal of Obstetrics and Gynecology*, 186 (5 Suppl Understanding), S228-31.

Koren, G., Madjunkova, S., & Maltepe, C. 2014. The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome--a systematic review. *Reproductive Toxicology*, 47, 77-80.

Koren, G., & Maltepe, C. 2004. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 24 (5), 530-533.

Koren, G., Ornoy, A., & Berkovitch, M. 2018. Hyperemesis gravidarum-is it a cause of abnormal fetal brain development? *Reproductive Toxicology*, 79, 84-88.

Koren, G., Piwko, C., Ahn, E., Boskovic, R., Maltepe, C., Einarson, A., Navioz, Y., & Ungar, W. J. 2005. Validation studies of the pregnancy-unique quantification of emesis (PUQE) scores. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 25 (3), 241-244.

Korevaar, T. I., Steegers, E. A., de Rijke, Y. B., Schalekamp-Timmermans, S., Visser, W. E., Hofman, A., Jaddoe, V. W., Tiemeier, H., Visser, T. J., Medici, M., & Peeters, R. P. 2015. Reference ranges and determinants of total hCG levels during pregnancy: The generation R study. *European Journal of Epidemiology*, 30 (9), 1057-1066.

Koudijs, H. M., Savitri, A. I., Browne, J. L., Amelia, D., Baharuddin, M., Grobbee, D. E., & Uiterwaal, C. S. 2016. Hyperemesis gravidarum and placental dysfunction disorders. *BMC Pregnancy and Childbirth*, 16 (1), 374.

Kramer, J., Bowen, A., Stewart, N., & Muhajarine, N. 2013. Nausea and vomiting of pregnancy: Prevalence, severity and relation to psychosocial health. *MCN. the American Journal of Maternal Child Nursing*, 38 (1), 21-27.

Kuo, S. H., Yang, Y. H., Wang, R. H., Chan, T. F., & Chou, F. H. 2010. Relationships between leptin, HCG, cortisol, and psychosocial stress and nausea and vomiting throughout pregnancy. *Biological Research for Nursing*, 12 (1), 20-27.

Kuru, O., Sen, S., Akbayir, O., Goksedef, B. P., Ozsurmeli, M., Attar, E., & Saygili, H. 2012. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Archives of Gynecology and Obstetrics*, 285 (6), 1517-1521.

Lacasse, A., & Bérard, A. 2008. Validation of the nausea and vomiting of pregnancy specific health related quality of life questionnaire. *Health and Quality of Life Outcomes*, 6, 32-7525-6-32.

Lacasse, A., Rey, E., Ferreira, E., Morin, C., & Bérard, A. 2008. Validity of a modified pregnancy-unique quantification of emesis and nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. *American Journal of Obstetrics and Gynecology*, 198 (1), 71.e1-71.e7.

Lagiou, P., Tamimi, R., Mucci, L. A., Trichopoulos, D., Adami, H. O., & Hsieh, C. C. 2003. Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: A prospective study. *Obstetrics and Gynecology*, 101 (4), 639-644.

Laitinen, L., Nurmi, M., Ellilä, P., Rautava, P., Koivisto, M., & Polo-Kantola, P. 2020. Nausea and vomiting of pregnancy: Associations with personal history of nausea and affected relatives. *Archives of Gynecology and Obstetrics*, 302 (4), 947-955.

Laitinen, L., & Polo-Kantola, P. 2019. Hyperemesis gravidarum. *Duodecim; Lääketieteellinen Aikakauskirja*, 135 (15), 1385-1392.

Larsen, S., Haavaldsen, C., Bjelland, E. K., Dypvik, J., Jukic, A. M., & Eskild, A. 2018. Placental weight and birthweight: The relations with number of daily cigarettes and smoking cessation in pregnancy. A population study. *International Journal of Epidemiology*, 47 (4), 1141-1150.

Law, R., Maltepe, C., Bozzo, P., & Einarson, A. 2010. Treatment of heartburn and acid reflux associated with nausea and vomiting during pregnancy. *Canadian Family Physician*, 56 (2), 143-144.

Lawrence, J. B., Oxvig, C., Overgaard, M. T., Sottrup-Jensen, L., Gleich, G. J., Hays, L. G., Yates, J. R.,3rd, & Conover, C. A. 1999. The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. *Proceedings of the National Academy of Sciences of the United States of America*, 96 (6), 3149-3153.

Lee, J., Lee, K., Kim, M., Choi, B., Yoo, K., & Kim, Y. 2003. The correlation of leptin and hCG (human chorionic gonadotrophin) levels in the serum between women with hyperemesis gravidarum and normal control. *Fertility and Sterility*, 80, 251.

Leeman, L., Dresang, L. T. & Fontaine, P. 2016. Hypertensive Disorders of Pregnancy. *American Family Physician*, 93(2), 121-127.

Lei, Z. M., & Rao, C. V. 2001. Neural actions of luteinizing hormone and human chorionic gonadotropin. *Seminars in Reproductive Medicine*, 19 (1), 103-109.

Leleu, A., Cathelain, A., Rubod, C., Vandendriessche, D., Cosson, M., & Giraudet, G. 2021. Symptom related to Essure® and evolution after removal: Outcomes of retrospective cohort. *Journal of Gynecology Obstetrics and Human Reproduction*, 50 (3), 101836.

Lenz, W., Pfeiffer, R. A., Kosenow, W & Hayman D. J. 1962. Thalidomide and congenital abnormalities. *Lancet* 279 (7219), 45-46.

Lien, H. C., Sun, W. M., Chen, Y. H., Kim, H., Hasler, W., & Owyang, C. 2003. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 284 (3), G481-9.

Lindholm, E. S., Altman, D., Norman, M., & Blomberg, M. 2015. Health care consumption during pregnancy in relation to maternal body mass index: A Swedish population based observational study. *Journal of Obesity*, 2015, Epub <https://doi.org/10.1155/2015/215683>.

Lockwood, C. M., Grenache, D. G., & Gronowski, A. M. 2009. Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. *Thyroid : Official Journal of the American Thyroid Association*, 19 (8), 863-868.

London, V., Grube, S., Sherer, D. M., & Abulafia, O. 2017. Hyperemesis gravidarum: A review of recent literature. *Pharmacology*, 100 (3-4), 161-171.

Louik, C., Hernandez-Diaz, S., Werler, M. M., & Mitchell, A. A. 2006. Nausea and vomiting in pregnancy: Maternal characteristics and risk factors. *Paediatric and Perinatal Epidemiology*, 20 (4), 270-278.

Lu, Q. B., Wang, Z. P., Gao, L. J., Gong, R., Sun, X. H., Wang, M., & Zhao, Z. T. 2015. Nausea and vomiting in early pregnancy and the risk of neural tube defects: A case-control study. *Scientific Reports*, 5, 7674.

Lub-Moss, M. M., & Eurelings-Bontekoe, E. H. 1997. Clinical experience with patients suffering from hyperemesis gravidarum (severe nausea and vomiting during pregnancy): Thoughts about subtyping of patients, treatment and counseling models. *Patient Education and Counseling*, 31 (1), 65-75.

Maconochie, N., Doyle, P., Prior, S., & Simmons, R. 2007. Risk factors for first trimester miscarriage--results from a UK-population-based case-control study. *BJOG : An International Journal of Obstetrics and Gynaecology*, 114 (2), 170-186.

Magtira, A., Schoenberg, F. P., MacGibbon, K., Tabsh, K., & Fejzo, M. S. 2015. Psychiatric factors do not affect recurrence risk of hyperemesis gravidarum. *Journal of Obstetrics and Gynaecology Research*, 41 (4), 512-516.

Mangili, G., Giorgione, V., Gentile, C., Bergamini, A., Pella, F., Almirante, G., & Candiani, M. 2014. Hydatidiform mole: Age-related clinical presentation and high rate of severe complications in older women. *Acta Obstetricia Et Gynecologica Scandinavica*, 93 (5), 503-507.

Mansour, G. M., & Nashaat, E. H. 2009. Helicobacter pylori and hyperemesis gravidarum. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 106 (1), 63-64.

Mansour, G. M., & Nashaat, E. H. 2011. Role of helicobacter pylori in the pathogenesis of hyperemesis gravidarum. *Archives of Gynecology and Obstetrics*, 284 (4), 843-847.

Markl, G. E., Strunz-Lehner, C., Egen-Lappe, V., Lack, N., & Hasford, J. 2008. The association of psychosocial factors with nausea and vomiting during pregnancy. *Journal of Psychosomatic Obstetrics and Gynaecology*, 29 (1), 17-22.

Matsuo, K., Ushioda, N., Nagamatsu, M., & Kimura, T. 2007. Hyperemesis gravidarum in Eastern Asian population. *Gynecologic and Obstetric Investigation*, 64 (4), 213-216.

Mayer, K. H., & McGill, A. L. 2019. Second-trimester fetal loss in a patient with hyperemesis gravidarum complicated by refeeding syndrome. *Obstetrics and Gynecology*, 133 (6), 1167-1170.

Mazzotta, P., Stewart, D., Atanackovic, G., Koren, G., & Magee, L. A. 2000. Psychosocial morbidity among women with nausea and vomiting of pregnancy: Prevalence and association with anti-emetic therapy. *Journal of Psychosomatic Obstetrics and Gynaecology*, 21 (3), 129-136.

Mazzotta, P., Stewart, D. E., Koren, G., & Magee, L. A. 2001. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. *Journal of Psychosomatic Obstetrics and Gynaecology*, 22 (1), 7-12.

McBride, W. G. 1961. Thalidomide and congenital malformations. *Lancet* 278 (7216), 1358.

McCarthy, F. P., Khashan, A. S., North, R. A., Moss-Morris, R., Baker, P. N., Dekker, G., Poston, L., Kenny, L. C., & SCOPE Consortium. 2011. A prospective cohort study investigating associations between hyperemesis gravidarum and cognitive, behavioural and emotional well-being in pregnancy. *PloS One*, 6 (11), e27678.

McParlin, C., Carrick-Sen, D., Steen, I. N., & Robson, S. C. 2016. Hyperemesis in pregnancy study: A pilot randomised controlled trial of midwife-led outpatient care. *European Journal of Obstetrics Gynecology and Reproductive Biology*, 200, 6-10.

McParlin, C., O'Donnell, A., Robson, S. C., Beyer, F., Moloney, E., Bryant, A., Bradley, J., Muirhead, C. R., Nelson-Piercy, C., Newbury-Birch, D., Norman, J., Shaw, C., Simpson, E., Swallow, B., Yates, L., & Vale, L. 2016. Treatments for hyperemesis gravidarum and nausea and vomiting in

pregnancy: A systematic review. *Journal of the American Medical Association*, 316 (13), 1392-1401.

Meighan, M., & Wood, A. F. 2005. The impact of hyperemesis gravidarum on maternal role assumption. *Journal of Obstetric, Gynecologic, and Neonatal Nursing : JOGNN / NAACOG*, 34 (2), 172-179.

Meinich, T., & Trovik, J. 2020. Early maternal weight gain as a risk factor for SGA in pregnancies with hyperemesis gravidarum: A 15-year hospital cohort study. *BMC Pregnancy and Childbirth*, 20 (1), 255.

Meltzer-Brody, S., Maegbaek, M. L., Medland, S. E., Miller, W. C., Sullivan, P., & Munk-Olsen, T. 2017. Obstetrical, pregnancy and socio-economic predictors for new-onset severe postpartum psychiatric disorders in primiparous women. *Psychological Medicine*, 47 (8), 1427-1441.

Minagawa, M., Narita, J., Tada, T., Maruyama, S., Shimizu, T., Bannai, M., Oya, H., Hatakeyama, K., & Abo, T. 1999. Mechanisms underlying immunologic states during pregnancy: Possible association of the sympathetic nervous system. *Cellular Immunology*, 196 (1), 1-13.

Mishriky, B. M., & Habib, A. S. 2012. Metoclopramide for nausea and vomiting prophylaxis during and after caesarean delivery: A systematic review and meta-analysis. *British Journal of Anaesthesia*, 108 (3), 374-383.

Mitchell, S. J., & Cox, P. 2017. ECG changes in hyperemesis gravidarum. *BMJ Case Reports*, Epub, <https://doi.org/10.1136/bcr-2016-217158>.

Mitchell-Jones, N., Gallos, I., Farren, J., Tobias, A., Bottomley, C., & Bourne, T. 2017. Psychological morbidity associated with hyperemesis gravidarum: A systematic review and meta-analysis. *BJOG : An International Journal of Obstetrics and Gynaecology*, 124 (1), 20-30.

Mitchell-Jones, N., Lawson, K., Bobdiwala, S., Farren, J. A., Tobias, A., Bourne, T., & Bottomley, C. 2020. Association between hyperemesis gravidarum and psychological symptoms, psychosocial outcomes and infant bonding: A two-point prospective case-control multicentre survey study in an inner city setting. *BMJ Open*, 10 (10), Epub, <https://doi.org/10.1136/bmjopen-2020-039715>.

Mittal, R., Debs, L. H., Patel, A. P., Nguyen, D., Patel, K., O'Connor, G., Grati, M., Mittal, J., Yan, D., Eshraghi, A. A., Deo, S. K., Daunert, S., & Liu, X. Z. 2017. Neurotransmitters: The critical modulators regulating gut-brain axis. *Journal of Cellular Physiology*, 232 (9), 2359-2372.

Moffett, P. M., Cartwright, L., Grossart, E. A., O'Keefe, D., & Kang, C. S. 2016. Intravenous ondansetron and the QT interval in adult emergency department patients: An observational study. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*, 23 (1), 102-105.

Morgan, S. R., Long, L., Johns, J., Angwin, C., Maitra, S., & Ross, J. A. 2017. Are early pregnancy complications more common in women with hyperemesis gravidarum? *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 37 (3), 355-357.

Mullin, P. M., Ching, C., Schoenberg, F., MacGibbon, K., Romero, R., Goodwin, T. M., & Fejzo, M. S. 2012. Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 25 (6), 632-636.

Munch, S. 2002. Chicken or the egg? the biological-psychological controversy surrounding hyperemesis gravidarum. *Social Science & Medicine*, 55 (7), 1267-1278.

Munch, S., Korst, L. M., Hernandez, G. D., Romero, R., & Goodwin, T. M. 2011. Health-related quality of life in women with nausea and vomiting of pregnancy: The importance of psychosocial context. *Journal of Perinatology : Official Journal of the California Perinatal Association*, 31 (1), 10-20.

Murphy, A., McCarthy, F. P., McElroy, B., Khashan, A. S., Spillane, N., Marchocki, Z., Sarkar, R. K., & Higgins, J. R. 2016. Day care versus inpatient management of nausea and vomiting of pregnancy: Cost utility analysis of a randomised controlled trial. *European Journal of Obstetrics Gynecology and Reproductive Biology*, 197, 78-82.

Nana, M., Tydeman, F., Bevan, G., Boulding, H., Kavanagh, K., Dean, C., & Williamson, C. 2021. Hyperemesis gravidarum is associated with increased rates of termination of pregnancy and suicidal ideation: Results from a survey completed by >5000 participants. *American Journal of Obstetrics and Gynecology*, 224 (6), 629-631.

Ndungu, J. R., Amayo, A., Qureshi, Z. P., & Kigondu, C. S. 2009. Gestational thyrotoxicosis associated with emesis in early pregnancy. *East African Medical Journal*, 86 (2), 55-58.

Nelson-Piercy, C., Fayers, P., & de Swiet, M. 2001. Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. *BJOG : An International Journal of Obstetrics and Gynaecology*, 108 (1), 9-15.

Ng, Q. X., Venkatanarayanan, N., De Deyn, M. L. Z. Q., Ho, C. Y. X., Mo, Y., & Yeo, W. S. 2018. A meta-analysis of the association between helicobacter pylori (H. pylori) infection and hyperemesis gravidarum. *Helicobacter*, 23 (1), e12455.

Niemeijer, M. N., Grooten, I. J., Vos, N., Bais, J. M., van der Post, J. A., Mol, B. W., Roseboom, T. J., Leeflang, M. M., & Painter, R. C. 2014. Diagnostic markers for hyperemesis gravidarum: A systematic review and metaanalysis. *American Journal of Obstetrics and Gynecology*, 211 (2), 150.e1-150.15.

Nijsten K., Dean C., van der Minnen L. M., Bais J. M. J., Ris-Stalpers C., van Eekelen R., Bremer H. A., van der Ham D. P., Heidema W. M., Huisjes A., Kleiverda, G., Kuppens, S., van Laar, J., Langenveld, J., van der Made, F., Papatsonis, D., Pelinck, M., Pernet, P. J., van Rheenen-Flach, L., Rijnders, R. J., Scheepers, H., Vogelvang, T., Mol, B., Roseboom, T. J., Koot, M. H., Grooten, I. J. & Painter, R. C. 2021 a. Recurrence, postponing pregnancy, and termination rates after hyperemesis gravidarum: Follow up of the MOTHER study. *Acta Obstetricia et Gynecologica Scandinavica*, 100(8), 1636-1643.

Nijsten K., Koot, M. H., van der Post, J. A. M., Bais J. M. J., Ris-Stalpers C., Naaktgeboren, C., Bremer H. A., van der Ham D. P., Heidema W. M., Huisjes A., Kleiverda, G., Kuppens, S., van Laar, J., Langenveld, J., van der Made, F., Papatsonis, D., Pelinck, M., Pernet, P. J., van Rheenen-Flach, L., Rijnders, R. J., Scheepers, H., Siegelaar, S. E., Vogelvang, T., Mol, B. W., Roseboom, T. J., Grooten, I. J. & Painter, R. C. 2021 b. Thyroid-stimulating hormone and free thyroxine fail to predict the severity and clinical course of hyperemesis gravidarum: A prospective cohort study. *Acta Obstetricia et Gynecologica Scandinavica*, 100(8), 1419-1429.

Nulman, I., Rovet, J., Barrera, M., Knittel-Keren, D., Feldman, B. M., & Koren, G. 2009. Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and diclectin. *The Journal of Pediatrics*, 155 (1), 45-50, 50.e1-2.

Nurmi, M. (2011). Lopu jo!: Apua raskauspahoinvointiin. (Master's thesis).Turku University of Applied Sciences.

Nurmi, M. (2014). Kääntäjä ja terveystiedon lukutaito: Erikoisalan sanasto vieraskielisen erikoisalan tekstin ymmärtämisen apuna. (Master's thesis). Turku: University of Turku.

Nurmi, M. (2020). Lopu jo! (An NVP information website in Finnish). <http://lopujo.fi/> Date of access: February 1, 2021.

Nurmi, M., Rautava, P., Gissler, M., Vahlberg, T & Polo-Kantola, P. (2018). Recurrence patterns of hyperemesis gravidarum. *American Journal of Obstetrics and Gynecology*, 219:469.e1–10.

Nurmi, M., Rautava, P., Gissler, M., Vahlberg, T & Polo-Kantola, P. (2020). Incidence and risk factors of hyperemesis gravidarum: A national register-based study in Finland, 2005–2017. *Acta Obstetricia et Gynecologica Scandinavica*, 99(8):1003–1013.

Nurmi, M., Rautava, P., Gissler, M., Vahlberg, T & Polo-Kantola, P. (2022). Readmissions due to Hyperemesis Gravidarum : a nation-wide Finnish register study. *Archives of Gynecology and Obstetrics.* Online ahead of print. Epub, <https://doi.org /10.1007/s00404-022-06448-w>.

Ogawa, K., Jwa, S. C., Kobayashi, M., Morisaki, N., Sago, H., & Fujiwara, T. 2017. Validation of a food frequency questionnaire for Japanese pregnant women with and without nausea and vomiting in early pregnancy. *Journal of Epidemiology*, 27 (5), 201-208.

Ohlsson, B., & Janciauskiene, S. 2007. New insights into the understanding of gastrointestinal dysmotility. *Drug Target Insights*, 2, 229-237.

Oruc, A. S., Mert, I., Akturk, M., Aslan, E., Polat, B., Buyukkagnici, U., & Danisman, N. 2013. Ghrelin and motilin levels in hyperemesis gravidarum. *Archives of Gynecology and Obstetrics*, 287 (6), 1087-1092.

Oudman, E., Wijnia, J. W., Oey, M., van Dam, M., Painter, R. C., & Postma, A. 2019. Wernicke's encephalopathy in hyperemesis gravidarum: A systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 236, 84-93.

Owe, K. M., Stoer, N., Wold, B. H., Magnus, M. C., Nystad, W., & Vikanes, A. V. 2019. Leisure-time physical activity before pregnancy and risk of hyperemesis gravidarum: A population-based cohort study. *Preventive Medicine*, 125, 49-54.

Ozturk, G., Ozgu-Erdinc, A. S., Ucar, F., Ginis, Z., Erden, G., & Danisman, N. 2017. Concentrations of prealbumin and some appetite-controlling hormones in pregnancies associated with hyperemesis gravidarium. *Annals of Clinical Biochemistry*, 54 (2), 258-263.

Panesar, N. S., Li, C. Y., & Rogers, M. S. 2001. Are thyroid hormones or hCG responsible for hyperemesis gravidarum? A matched paired study in pregnant Chinese women. *Acta Obstetricia Et Gynecologica Scandinavica*, 80 (6), 519-524.

Patel, A., Felstead, D., Doraiswami, M., Stocks, G. M., & Waheed, U. 2011. Acute starvation in pregnancy: A cause of severe metabolic acidosis. *International Journal of Obstetric Anesthesia*, 20 (3), 253-256.

Patel, J. 2013. Droperidol- and ondansetron-induced life-threatening arrhythmias. *Journal of Emergency Nursing*, 39 (4), 393-394.

Peled, Y., Melamed, N., Hiersch, L., Hadar, E., Wiznitzer, A., & Yogev, Y. 2013. Pregnancy outcome in hyperemesis gravidarum - the role of fetal gender. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 26 (17), 1753-1757.

Peled, Y., Melamed, N., Krissi, H., Eitan, R., Yogev, Y., & Pardo, J. 2012. The impact of severe hyperemesis gravidarum on the triple test screening results. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 25 (6), 637-638.

Petersen, I., McCrea, R. L., Lupattelli, A., & Nordeng, H. 2015. Women's perception of risks of adverse fetal pregnancy outcomes: A large-scale multinational survey. *BMJ Open*, 5 (6), e007390-2014-007390.

Petry, C. J., Ong, K. K., Burling, K. A., Barker, P., Goodburn, S. F., Perry, J. R. B., Acerini, C. L., Hughes, I. A., Painter, R. C., Afink, G. B., Dunger, D. B., & O'Rahilly, S. 2018. Associations of vomiting and antiemetic use in pregnancy with levels of circulating GDF15 early in the second trimester: A nested case-control study. *Wellcome Open Research*, 3, 123.

Pintican, D., Poienar, A. A., Strilciuc, S., & Mihu, D. 2019. Effects of maternal smoking on human placental vascularization: A systematic review. *Taiwanese Journal of Obstetrics & Gynecology*, 58 (4), 454-459.

Piwko, C., Koren, G., Babashov, V., Vicente, C., & Einarson, T. R. 2013. Economic burden of nausea and vomiting of pregnancy in the USA. *Journal of Population Therapeutics and Clinical Pharmacology*, 20 (2), e149-60.

Poursharif, B., Korst, L. M., Fejzo, M. S., MacGibbon, K. W., Romero, R., & Goodwin, T. M. 2008. The psychosocial burden of hyperemesis gravidarum. *Journal of Perinatology : Official Journal of the California Perinatal Association*, 28 (3), 176-181.

Poursharif, B., Korst, L. M., Macgibbon, K. W., Fejzo, M. S., Romero, R., & Goodwin, T. M. 2007. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. *Contraception*, 76 (6), 451-455.

Price, C. J., Hoyda, T. D., & Ferguson, A. V. 2008. The area postrema: A brain monitor and integrator of systemic autonomic state. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 14 (2), 182-194.

PubMed. (2021). PubMed, US national library of medicine. <https://www.ncbi.nlm.nih.gov/pubmed> Date of access: May 7, 2021.

Ramskold, L. A., & Asaria, R. H. 2012. Valsalva retinopathy secondary to hyperemesis gravidarum. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 162 (1), 118-119.

Roseboom, T. J., Ravelli, A. C., van der Post, J. A., & Painter, R. C. 2011. Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 156 (1), 56-59.

Roseboom, T. J., van der Meulen, J. H., Osmond, C., Barker, D. J., Ravelli, A. C., Schroeder-Tanka, J. M., van Montfrans, G. A., Michels, R. P., & Bleker, O. P. 2000. Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart*, 84 (6), 595-598.

Royal College of Obstetricians and Gynaecologists. (2016). The management of nausea and vomiting of pregnancy and hyperemesis gravidarum. green-top guideline no. 69. <https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf> Date of access: October 16, 2020.

Sandven, I., Abdelnoor, M., Nesheim, B. I., & Melby, K. K. 2009. Helicobacter pylori infection and hyperemesis gravidarum: A systematic review and meta-analysis of case-control studies. *Acta Obstetricia Et Gynecologica Scandinavica*, 88 (11), 1190-1200.

Sandven, I., Abdelnoor, M., Wethe, M., Nesheim, B. I., Vikanes, A., Gjonnes, H., & Melby, K. K. 2008. Helicobacter pylori infection and hyperemesis gravidarum. an institution-based case-control study. *European Journal of Epidemiology*, 23 (7), 491-498.

Scarborough, A., Kemp, O., & Scarborough, O. 2020. Spontaneous pneumomediastinum secondary to hyperemesis gravidarum: A case report and principles of recognition and management. *Case Reports in Women's Health*, 28, e00257.

Scott, C. L., Chavez, G. F., Atrash, H. K., Taylor, D. J., Shah, R. S., & Rowley, D. 1997. Hospitalizations for severe complications of pregnancy, 1987-1992. *Obstetrics and Gynecology*, 90 (2), 225-229.

Sharifzadeh, F., Kashanian, M., Koohpayehzadeh, J., Rezaian, F., Sheikhansari, N., & Eshraghi, N. 2018. A comparison between the effects of ginger, pyridoxine (vitamin B6) and placebo for the treatment of the first trimester nausea and vomiting of pregnancy (NVP). *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, 31 (19), 2509-2514.

Sharp, B. R., Sharp, K. M., Patterson, B., & Dooley-Hash, S. 2016. Treatment of nausea and vomiting in pregnancy: Factors associated with ED revisits. *The Western Journal of Emergency Medicine*, 17 (5), 585-590.

Shrady, G. F., & Stedman, T. L. (Eds.). (1888). Medical record, volume 33. W. Wood, New York.

Simpson, S. W., Goodwin, T. M., Robins, S. B., Rizzo, A. A., Howes, R. A., Buckwalter, D. K., & Buckwalter, J. G. 2001. Psychological factors and hyperemesis gravidarum. *Journal of Women's Health & Gender-Based Medicine*, 10 (5), 471-477.

Sipponen, P. 1997. Helicobacter pylori gastritis--epidemiology. *Journal of Gastroenterology*, 32 (2), 273-277.

Temkin, O. & Soranus (1991). Soranus' gynecology. Johns Hopkins University Press, Baltimore.

Soto-Wright, V., Bernstein, M., Goldstein, D. P., & Berkowitz, R. S. 1995. The changing clinical presentation of complete molar pregnancy. *Obstetrics and Gynecology*, 86 (5), 775-779.

Steinberg, B. J., Hilton, I. V., Iida, H., & Samelson, R. 2013. Oral health and dental care during pregnancy. *Dental Clinics of North America*, 57 (2), 195-210.

Stokke, G., Gjelsvik, B. L., Flaatten, K. T., Birkeland, E., Flaatten, H., & Trovik, J. 2015. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: A 10-year retrospective cohort study. *Acta Obstetricia Et Gynecologica Scandinavica*, 94 (4), 359-367.

Strachan, B. K., Jokhi, R. P., & Filshie, G. M. 2000. Persistent hyperemesis gravidarum and helicobacter pylori. *Journal of Obstetrics & Gynaecology*, 20 (4), 427-427.

Summers, A. 2012. Emergency management of hyperemesis gravidarum. *Emergency Nurse : The Journal of the RCN Accident and Emergency Nursing Association*, 20 (4), 24-28.

Sun, S., Qiu, X., & Zhou, J. 2014. Clinical analysis of 65 cases of hyperemesis gravidarum with gestational transient thyrotoxicosis. *The Journal of Obstetrics and Gynaecology Research*, 40 (6), 1567-1572.

Sund, R. 2012. Quality of the Finnish hospital discharge register: A systematic review. *Scandinavian Journal of Public Health*, 40 (6), 505-515.

Suzuki, S., Igarashi, M., Yamashita, E., & Satomi, M. 2009. Ptyalism gravidarum. *North American Journal of Medical Sciences*, 1 (6), 303-304.

Swallow, B. L., Lindow, S. W., Masson, E. A., & Hay, D. M. 2005. Women with nausea and vomiting in pregnancy demonstrate worse health and are adversely affected by odours. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 25 (6), 544-549.

Syn, N. L., Chan, S. Y., Chia, E. W. Y., Ong, W. X., Phua, D., Cai, S., Shek, L. P. C., Chong, Y. S., Daniel, L. M., Broekman, B. F. P., Godfrey, K. M., Meaney, M. J., & Law, E. C. 2021. Severity of nausea and vomiting in pregnancy and early childhood neurobehavioural outcomes: The growing up in Singapore towards healthy outcomes study. *Paediatric and Perinatal Epidemiology*, 35 (1), 98-108.

Tan, P. C., Jacob, R., Quek, K. F., & Omar, S. Z. 2006. Readmission risk and metabolic, biochemical, haematological and clinical indicators of severity in hyperemesis gravidarum *The Australian & New Zealand Journal of Obstetrics & Gynaecology*, 46 (5), 446-450.

Tan, P. C., Jacob, R., Quek, K. F., & Omar, S. Z. 2007. Pregnancy outcome in hyperemesis gravidarum and the effect of laboratory clinical indicators of hyperemesis severity. *The Journal of Obstetrics and Gynaecology Research*, 33 (4), 457-464.

Tan, P. C., Tan, N. C., & Omar, S. Z. 2009. Effect of high levels of human chorionic gonadotropin and estradiol on the severity of hyperemesis gravidarum. *Clinical Chemistry and Laboratory Medicine : CCLM / FESCC*, 47 (2), 165-171.

Taylor, C. E. 2016. A novel treatment for "morning sickness": Nausea of pregnancy could be induced by excess sulfite which molybdenum can help alleviate. *Medical Hypotheses*, 95, 31-33.

The American College of Obstetricians and Gynecologists. 2018. ACOG practice bulletin no. 189 summary: Nausea and vomiting of pregnancy. *Obstetrics and Gynecology*, 131 (1), 190-193.

Tianyi, F. L., Agbor, V. N., & Njim, T. 2017. Metoclopramide induced acute dystonic reaction: A case report. *BMC Research Notes*, 10 (1), 32-016-2342-6.

Tincello, D. G., & Johnstone, M. J. 1996. Treatment of hyperemesis gravidarum with the 5-HT3 antagonist ondansetron (Zofran). *Postgraduate Medical Journal*, 72 (853), 688-689.

Topalahmetoglu, Y., Altay, M. M., Akdag Cirik, D., Tohma, Y. A., Colak, E., Coskun, B., & Gelisen, O. 2017. Depression and anxiety disorder in hyperemesis gravidarum: A prospective case-control study. *Turkish Journal of Obstetrics and Gynecology*, 14 (4), 214-219.

Trogstad, L. I., Stoltenberg, C., Magnus, P., Skjaerven, R., & Irgens, L. M. 2005. Recurrence risk in hyperemesis gravidarum. *BJOG : An International Journal of Obstetrics and Gynaecology*, 112 (12), 1641-1645.

Trovik, J., & Vikanes, A. 2016. Hyperemesis gravidarum is associated with substantial economic burden in addition to severe physical and psychological suffering. *Israel Journal of Health Policy Research*, 5, 43.

Tulmaç, Ö., Kılıç, R., Yaman, S., Aktulum, F., Şimşek, G., & Erdinç, S. 2021. Evaluation of the vestibular system with video head impulse test in pregnant women with hyperemesis gravidarum. *The Journal of Obstetrics and Gynaecology Research*, 47 (1), 96-102.

Tunc, S. Y., Agacayak, E., Budak, S., Tunc, N., Icen, M. S., Findik, F. M., Ekinci, A., & Gul, T. 2016. Serum levels of neopterin, inflammatory markers and oxidative stress indicators in hyperemesis gravidarum. *The Journal of Obstetrics and Gynaecology Research*, 42 (6), 618-624.

University of California Davis. (2020). A study of the effect of probiotics on gastrointestinal function during pregnancy. <https://www.clinicaltrials.gov/ct2/show/NCT03320226> Date of access: January 22, 2021.

Unsel, N., Benian, A., & Erel, C. T. 2004. Leptin levels in women with hyperemesis gravidarum. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 84 (2), 162-163.

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gotzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., Egger, M., & STROBE Initiative. 2014. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *International Journal of Surgery*, 12 (12), 1500-1524.

Vandraas, K., Vikanes, A., Vangen, S., Magnus, P., Støer, N., & Grjibovski, A. 2013. Hyperemesis gravidarum and birth outcomes-a population-based cohort study of 2.2 million births in the Norwegian birth registry. *BJOG : An International Journal of Obstetrics and Gynaecology*, 120(13), 1654-1660.

Vandraas, K. F., Grjibovski, A. M., Støer, N. C., Troisi, R., Stephansson, O., Ording, A. G., Vangen, S., Grotmol, T., & Vikanes, Å. 2015. Hyperemesis gravidarum and maternal cancer risk, a Scandinavian nested case-control study. *International Journal of Cancer*, 137 (5), 1209-1216.

Vandraas, K. F., Vikanes, A. V., Støer, N. C., Vangen, S., Magnus, P., & Grjibovski, A. M. 2013. Is hyperemesis gravidarum associated with placental weight and the placental weight-to-birth weight ratio? A population-based Norwegian cohort study. *Placenta*, 34 (11), 990-994.

Vargesson, N. 2015. Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Research. Part C, Embryo Today : Reviews*, 105 (2), 140-156.

Verberg, M. F., Gillott, D. J., Al-Fardan, N., & Grudzinskas, J. G. 2005. Hyperemesis gravidarum, a literature review. *Human Reproduction Update*, 11 (5), 527-539.

Vikanes, A., Grjibovski, A. M., Vangen, S., Gunnes, N., Samuelsen, S. O., & Magnus, P. 2010. Maternal body composition, smoking, and hyperemesis gravidarum. *Annals of Epidemiology*, 20 (8), 592-598.

Vikanes, A., Grjibovski, A. M., Vangen, S., & Magnus, P. 2008. Variations in prevalence of hyperemesis gravidarum by country of birth: A study of 900,074 pregnancies in Norway, 1967-2005. *Scandinavian Journal of Public Health*, 36 (2), 135-142.

Vikanes, A., Skjaerven, R., Grjibovski, A. M., Gunnes, N., Vangen, S., & Magnus, P. 2010. Recurrence of hyperemesis gravidarum across generations: Population based cohort study. *BMJ (Clinical Research Ed.)*, 340, c2050.

Vikanes, A. V., Stoer, N. C., Magnus, P., & Grjibovski, A. M. 2013. Hyperemesis gravidarum and pregnancy outcomes in the Norwegian mother and child cohort -- a cohort study. *BMC Pregnancy and Childbirth*, 13 (1), 169.

Vilming, B., & Nesheim, B. 2001. Hyperemesis gravidarum in a contemporary population in Oslo. *Acta Obstetricia Et Gynecologica Scandinavica*, 79 (8), 640-643.

Vlachodimitropoulou-Koumoutsea, E., Gosh, S., Manmatharajah, B., Ray, A., Igwe-Omoke, N., & Yoong, W. 2013. Pregnancy outcomes in severe hyperemesis gravidarum in a multi-ethnic population. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, 33 (5), 455-458.

Vogt Isaksen, C. 2004. Maternal smoking, intrauterine growth restriction, and placental apoptosis. *Pediatric and Developmental Pathology : The Official Journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*, 7 (5), 433-442.

Walch, A., Duke, M., Auty, T., & Wong, A. 2018. Profound hypokalaemia resulting in maternal cardiac arrest: A catastrophic complication of hyperemesis gravidarum? *Case Reports in Obstetrics and Gynecology*, 2018, 4687587.

Walsh, J. W., Hasler, W. L., Nugent, C. E., & Owyang, C. 1996. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. *The American Journal of Physiology*, 270 (3 Pt 1), G506-14.

Weigel, M. M., Caiza, M. E., Lascano, Y., Barreno, G., & Mosquera, L. 2000. Early pregnancy nausea and vomiting in a high-altitude Andean population. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 69 (1), 9-21.

World Health Organization 2012 The international statistical classification of diseases and related health problems, ICD-10 release 2010. <http://apps.who.int/classifications/icd10/browse/2010/en#/O21> Date of access: November 21, 2012.

World Health Organization 2016. The international statistical classification of diseases and related health problems, ICD-10 release 2016. <http://apps.who.int/classifications/icd10/browse/2016/en#/O21> Date of access: October 4, 2016.

World Health Organization 2020. The international statistical classification of diseases and related health problems, ICD-11 release 2020 a. <https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1745892781> Date of access: May 26, 2020.

World Health Organization. 2020 b. Sex ratio. <http://origin.searo.who.int/entity/health_situation_trends/data/chi/sex-ratio/en/> Date of access: October 15, 2020.

Wright, L. B., Schoemaker, M. J., Jones, M. E., Ashworth, A., & Swerdlow, A. J. 2018. Breast cancer risk in relation to history of preeclampsia and hyperemesis gravidarum: Prospective analysis in the generations study. *International Journal of Cancer*, 143 (4), 782-792.

Yilmaz, S., Akdag Cirik, D., Demirtas, C., Timur, H., Sahin, A., Danisman, N., & Uygur, D. 2016. Do vitamin D and high-sensitivity-C reactive protein levels differ in patients with hyperemesis gravidarum? A preliminary study. *Turkish Journal of Obstetrics and Gynecology*, 13 (3), 123-126.

Zanchi, D., Depoorter, A., Egloff, L., Haller, S., Mahlmann, L., Lang, U. E., Drewe, J., Beglinger, C., Schmidt, A., & Borgwardt, S. 2017. The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review. *Neuroscience and Biobehavioral Reviews*, 80, 457-475.

Zeitlin, J., Durox, M., Macfarlane, A., Alexander, S., Heller, G., Loghi, M., Nijhuis, J., Sól Ólafsdóttir, H., Mierzejewska, E., Gissler, M., Blondel, B. & the Euro-Peristat Network 2021. Using Robson's Ten-Group Classification System for comparing caesarean section rates in Europe: an analysis of routine data from the Euro-Peristat study. *BJOG : An International Journal of Obstetrics and Gynaecology*. 128 (9), 1444-1453.

Zhang, J., & Cai, W. W. 1991. Severe vomiting during pregnancy: Antenatal correlates and fetal outcomes. *Epidemiology*, 2 (6), 454-457.

Zhang, Y., Cantor, R. M., Macgibbon, K., Romero, R., Goodwin, T. M., Mullin, P. M., & Fejzo, M. S. 2010. Familial aggregation of hyperemesis gravidarum. *American Journal of Obstetrics and Gynecology*, 204 (3), 230.e1-e7.

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