Causes of hyperemesis gravidarum

by

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PREFACE

The first time a patient with hyperemesis gravidarum (hyperemesis) captured my attention was in 1994, during my work as resident at the Department of Gynecology and Obstetrics at Buskerud Hospital Trust. A young immigrant woman of Turkish origin, expecting her first child, had severe hyperemesis resistant to all antiemetic treatment. She ended up with parenteral nutrition for 82 days. I had several discussions with Sverre Stray-Pedersen, Head of the Department and my mentor, on possible explanations for her long-lasting and severe hyperemesis. He encouraged me to start research on the causality of hyperemesis. Additionally he insisted that research was an obligation for every medical doctor. He gave me the following challenge: *"Are you just going to receive a monthly pay check and not contribute with new knowledge?"*

It took me ten years before I started research on hyperemesis. During this time I admitted many severely ill hyperemesis patients to hospital and realized that we knew very little about its causes as well as consequences. Tragically, Sverre passed away during this period of time and could therefore not be a part of this research. Fortunately, however, we had colleagues who strongly believed that research on hyperemesis might be of value. First in line was my long-time colleague as an emergency room doctor in the municipality of Bærum, Per Magnus. Without his support, advice and encouragement, this work had not been possible to complete.

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First and foremost I want to thank my main supervisor, Per Magnus at NIPH, for introducing me to the field of epidemiology. During the work with this thesis we have had many fruitful discussions, and I am truly grateful for his encouragement and valuable comments.

I also want to thank my two co-advisers and co-authors Siri Vangen and Andrej Grjibovski. Siri is a pioneer in research regarding perinatal health among immigrants to Norway and has generously shared her knowledge with me. Andrej has with his loyal support and tremendous working capacity contributed vastly to this thesis. He was even the first author of the third paper. Both co-advisors have been available for planning of publications, as well as participating in the statistical analysis and the writing process. Their contributions have been of invaluable importance.

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Finally, I won't fail to thank my close friends at NIPH, Else-Karin Grøholt, Lill Trogstad and Merete Eggesbø. Whether it comes to discussing research or private matters, they are always present with a lot of warmth, humor and genuine care. I am truly grateful for having them in my life.

Last but not least, I want to thank my husband, Tor, for his everlasting, never-ending care, enthusiasm and support.

Oslo, December 2009

Åse Vikanes

DEFINITIONS AND ABBREVIATIONS

AD: Anno Domini

aOR: Adjusted odds ratio

BC: Before Christ

BMI: Body mass index, kg/m^2

CI: Confidence interval

cOR: Crude odds ratio

Ethnic Norwegian: A person who was born in Norway to parents who were born in Norway

Immigrant: A person who has moved to Norway (before October 1st 2008 categorized as first generation immigrant)

GEE: Generalized estimating equations

hCG: Human Chorionic Gonadotropin

Hyperemesis: Hyperemesis gravidarum

HP: Helicobacter pylori

ICD: International Classification of Diseases

LBW: Low birth weight, defined as birth weight < 2500 grams

MBRN: The Medical Birth Registry of Norway

MoBa: The Norwegian Mother and Child Cohort

NIPH: Norwegian Institute of Public Health

Norwegian born immigrant: A person born in Norway with two immigrant parents (before October 1st 2008 categorized as second generation immigrants)

QOL: Quality of life

RR: Relative risk

SES: Socio-economic status

1. INTRODUCTION

The vomiting reflex is present in many species ranging from fish to higher mammals and has from an evolutionary perspective prevented species from ingesting toxins (1). In humans, the motor-reflex response of vomiting is often preceded by the unpleasant sensation of nausea triggered by different input mechanisms under various conditions (2). The central nervous system plays a critical role in the physiology of nausea and vomiting, by being the primary site that receives and processes the various emetic stimuli. Nausea and vomiting in pregnancy is previously been interpret as a mechanism to protect against teratogenic, mutagenic and abortifacient chemicals (3, 4). Like in humans, monkeys and dogs have been reported to have anorexia in pregnancy (5).

While nausea and vomiting in pregnancy occurs in up to 80% of all pregnancies, hyperemesis represents a more severe condition by different authors reported to affect 0.5-3.2% of pregnant women (6). Hyperemesis is the most common reason for hospitalization in early pregnancy, and is associated with adverse pregnancy outcomes, such as preterm birth and low birth weight (7-9). The etiology of hyperemesis is largely unknown. The main aim of this thesis is to contribute to our understanding of the primary causes of hyperemesis. Before possible causes are discussed further, a description of clinical features and previously suggested pathogenic mechanisms is presented.

1.1. Historical understanding of hyperemesis gravidarum

Whereas nausea and vomiting were first described as symptoms of early pregnancy in Egypt 2000 BC, hyperemesis was probably first described during the 2nd century AD (10-12). One particular papyrus is currently exhibited at the Petrie Museum of Egyptian Archeology in London (12). Many authors have speculated about the causes of nausea and vomiting in pregnancy through historical time (13, 14).

Hippocrates (460-377 BC) as well as Aristotle (384-322 BC) observed that the degree of nausea and vomiting could be related to fetal gender (15). Hippocrates stated in his "Aphorisms" that a woman pregnant with a female fetus would have an unhealthy pale

appearance, freckled face, enlarged left breast and downward-turned nipples. Soranus (98-138 AD), a physician from Ephesus, concluded in his "Gynecology" that although these forecasts were plausible, the opposite might well happen. Throughout the period of Antiquity, boys were strongly preferred and families would much appreciate the correct prediction of the fetal sex (15). Soranus as well as the Greek medical author Paulus of Egina (625-690 AD) were both aware of the severe forms of nausea and vomiting in pregnancy described as "vomitus aciduus". What all authors during the period of Antiquity had in common, was the idea that vomiting was caused by retained menstrual blood and abnormal accumulation of fluid in the stomach (11).

The first fatal cases of hyperemesis in the medical literature were reported by Kerkring in 1706 and by Dance in 1827 (11, 16). One of history's most famous fatal cases was the English writer Charlotte Brontë (1816-1855), author of the novel "Jane Eyre". Her condition was explained as a neurosis caused by rejection of her pregnancy and femininity. However, an analysis of Charlotte Brontë's last months casts doubts as to to whether she actually was pregnant (17). In 1891, Kaltenbach presented a paper based on negative findings from post mortem examinations of hyperemesis patients in "Deutsche Gesellschaft für Gynekologie und Geburtshilfe" in Berlin. He suggested that the condition was caused by the woman's underlying unconscious rejection of the child and the husband (11, 18).

The explanations of nausea and vomiting in pregnancy have changed over time. The time period until 1929 has been named "the early somatic era". The period lasting from 1930 to 1980 has been called the "intra-psychic era", and the time period after 1980 the "metabolic and social stress era" (19). During the intra-psychic era, denial of patient suffering was common. A publication from 1934 stated that the appropriate treatment of a patient suffering from severe symptoms was not to allow her an emesis basin. *"She is told that, in the event of not being able to control herself, she is to vomit into bed and the nurse is instructed not to be in hurry about changing her"* (20) . Fairweather suggested, as recent as 1968, that nausea and vomiting in pregnancy was associated with a hysterical personality and reduced intelligence (14). Even though current causal theories on the development of hyperemesis mainly focus on genetic or environmental factors, patients suffering from this disease are still told by their health-care providers to "quit pretending to be sick" (21).

In 1937, Ernst Schjøtt-Rivers wrote the only thesis presented so far on hyperemesis gravidarum in Norway. His thesis comprised a review of previous research, a study of visual disturbances, post mortem findings as well as some laboratory results (11).

1.2. Time trends

Several authors have claimed that the prevalence of hyperemesis decreased during the First and Second World War (16, 22, 23). In the periods 1938-39 and 1948-53, the prevalence of hyperemesis necessitating admission to hospital was 0.5-1% in Aberdeen City. The prevalence was lower during the wars and the immediate post-war years. The change in prevalence was explained by psychosocial influences, rather than changes in diet and food rationing. A husband being absent from home was considered to have a positive effect on the wife's nausea and vomiting symptoms (22). Some years later, the prevalence of hyperemesis was reported to have dropped from 2.4% in 1930 to 0.6% in 1960 (24). This was explained by the fact that patients during this time started to use anti-emetic drugs. Until the mid-twentieth century, 10-25% of the severe and neglected hyperemesis cases were reported to end with death of the patient (25, 26). From 1951 to 1960 the maternal mortality in the United Kingdom decreased from 1.59 to 0.3 per 100 000 deliveries. Better treatment of hyperemesis patients due to restoration of the fluid and electrolyte balance contributed vastly to the decrease in total maternal mortality (14, 27). Nevertheless, in Norway one woman died from malnutrition as a consequence of hyperemesis as recently as 2004 (28).

1.3. Definitions and clinical pictures

Over the years, the definition of hyperemesis has changed (29). This is reflected in the coding of the disease according to the International Classification of Diseases (ICD) as well as in the research reports on hyperemesis. Although nausea and vomiting in pregnancy is common and hyperemesis is rare, the two conditions have often been studied as part of the same continuum (30-33). Whether there is a gradual transition between the two or not, is not clear (29). The different ways of defining the clinical manifestations of hyperemesis may partly explain why previous research on this condition so far has reported conflicting or inconclusive results (29, 34).

Fairweather's criteria

In Fairweather's landmark paper from 1968, hyperemesis was described as "*pernicious vomiting of pregnancy or intractable vomiting and disturbed nutrition, such as alteration of electrolyte balance, loss of weight of 5% or more, ketosis and acetonuria, with ultimate neurological disturbances, liver damage, retinal haemorrhage and renal damage"* (14). This definition of hyperemesis was proposed by a committee appointed by the American Council on Pharmacy and Chemistry in 1956. In his review, however, Fairweather defined hyperemesis as "*vomiting occurring in pregnancy appearing for the first time before twentieth week of gestation, and of such severity as to require the patient's admission to hospital, the vomiting not being associated with coincidental conditions such as appendicitis, pyelitis etc*".

International Classification of Diseases (ICD)

In the Medical Birth Registry of Norway (MBRN), hyperemesis was registered from 1967 to 1998 according to the ICD 8th revision, and from 1999 and onwards according to the 10th revision (35). In ICD 8, hyperemesis was described as "Hyperemesis without mention of neuritis" [638.0] or "Hyperemesis with mention of neuritis" [638.9]. ICD 10 categorizes excessive vomiting in pregnancy starting before the end of the 22nd week of gestation as mild or unspecified hyperemesis [O 21.0] when there is no metabolic disturbance, and as a more severe form of hyperemesis [O21.1] when metabolic disturbances such as carbohydrate depletion, dehydration and electrolyte imbalance are present. Although not used by the MBRN, the ICD 9th revision was used in many other institutions, defining hyperemesis as excessive vomiting in pregnancy [643].

The Norwegian Society of Gynecology and Obstetrics (NFOG)

Pregnant women hospitalized in Norway with hyperemesis will be diagnosed according to guidelines made by the Norwegian Society of Obstetrics and Gynecology (NFOG) (36). These guidelines were last updated in 2008, and define hyperemesis as "persisting nausea and vomiting starting before 20th week of gestation and leading to reduced well-being, dehydration, weight loss and fluid and electrolyte disturbances". This definition of hyperemesis resembles the severe form of hyperemesis in ICD 10, O 21.1. According to NFOG, the diagnosis of hyperemesis is based on the exclusion of other underlying conditions (36).

1.4. Treatment

During the late 1950s, nausea and vomiting in pregnancy was one of several indications for treatment with the tranquillizer Thalidomide, later known to cause congenital malformations in 10 000 babies worldwide (37, 38). Due to the fear of possible teratogenic side effects, pregnant women as well as their physicians are still afraid to use drugs in pregnancies in general, and during the first trimester in particular (39). When women are admitted to hospital for hyperemesis in Norway, NFOG's guidelines for treatment will be followed (36). This treatment is based on cautious rehydration with intravenous fluid replacement, correction of electrolyte imbalance and vitamin deficiencies (first and foremost thiamine, or vitamin B_1, and folate) as well as antiemetic treatment. Antiemetic treatment may often be initiated with histamine-1-receptor antagonists such as meclozin and prometazin or dopamine-receptor-antagonists such as prochlorperazin or chlorpromazin. Pyridoxine (vitamin B_6), ginger, acupressure and acupuncture are sometimes recommended in milder forms of hyperemesis. For more therapeutically resistant cases, steroids such as metylprednisolon and serotonin-antagonists such as ondansetron might be the treatment of choice. For the most severe cases, naso-gastric feeding tubes, naso-duodenal tubes or parenteral nutrition will also be employed.

1.5. Consequences for the mother and the child

Quality of life

Nausea and vomiting in pregnancy and hyperemesis are both known to reduce a woman's quality of life (QOL) (21, 40). A recent American study reported 80% of women with hyperemesis to have reduced QOL (21). The severity of nausea and vomiting has been measured by a variety of questionnaires. Two of the latest are The Pregnancy Unique-Quantification of Emesis (PUQE) score and The Hyperemesis Impact of Symptoms Questionnaire (HIS) (41-49). The use of these tools has revealed that women with moderate to severe nausea and vomiting have QOL scores comparable to women with recent breast cancer, myocardial infarction or post partum depression (40). One study compared the intensity of symptoms among 160 pregnant women at 11 weeks of gestation to the intensity of nausea and vomiting experienced by patients receiving chemotherapy (43). The results showed that the intensity of "normal" nausea and vomiting at 11 weeks of gestation was comparable to the kind of nausea patients have experienced by moderately nausea-producing

chemotherapy. The authors stated: "*Just as the pain of labor was widely underestimated in the past and has been shown by objective pain ratings to be comparable to the worst pain experienced in other contexts, this study demonstrates that* nausea and vomiting *experienced by pregnant women are comparable to what is to be the worst nausea, that of cancer therapy*".

The consequences of nausea and vomiting in pregnancy on later fertility have been addressed in several studies (50-52). Women with severe symptoms are less able to welcome another pregnancy; in fact they are known to consider terminating the next pregnancy because of their sufferings.

Maternal conditions

Among the most commonly reported complications of hyperemesis is Wernicke's encephalopathy, resulting from vitamin B_1 (thiamine) deficiency (6, 25, 53). Also "wet" beriberi (echocardiographic findings and hemodynamic parameters) and "dry" beriberi (peripheral neuropathy or facial nerve neuropathy) due to vitamin B_1 deficiency have been described (54). Vitamin B_6 (pyridoxine) and B_{12} (cobalamin) deficiencies have also been causing peripheral neuropathies in relation to hyperemesis (6). Vitamin K deficiency has been reported to induce coagulopathy and bleeding diathesis in hyperemesis patients, followed by an increased risk of fetal intracranial hemorrhage and secondary hydrocephalus (55-57). Even retinal hemorrhage in relation to hyperemesis has been described (58).

Central pontine myelinolysis due to hyponatremia has been reported, as have vasospasms of the cerebral arteries due to possible sympathetic nerve stimulation and sinus venous thrombosis (59-61). Rupture of esophagus, pneumomediastinum, splenic avulsion, hepatorenal damage, rhabdomyelinolysis, gastroparesis, hypokalemic myopathy and death have been reported among hyperemesis patients (62-65).

Hyperemesis has also been described as a risk factor for the development of rheumatoid arthritis in later life (66). This might suggest that some immunological reactions are initiated in women suffering from hyperemesis.

Pregnancy outcomes

Discrepant results are found in studies related to hyperemesis and pregnancy outcomes, but the most notable trends are low birth weight, preterm birth and lower 5-minutes Apgar scores (67-76). A recent review on prediction of adverse pregnancy outcomes according to early pregnancy events reported that hyperemesis is associated with preterm deliveries, small for gestational age infants, low birth weight (LBW), very low birth weight (< 1500 grams) as well as low 5-min Apgar scores (69). Other studies did not report such findings (14, 30, 31, 77-80). On the contrary, some implied that hyperemesis is associated with beneficial pregnancy outcomes, such as reduced risk of pregnancy loss during the first trimester, increased birth weight, higher gestational age and lower proportion of preterm births (31, 78). As mentioned before, different study designs and inclusion criteria might explain the conflicting results, in addition to effects of confounders that have not been adjusted for.

Congenital malformations

Studies of congenital malformations have shown conflicting results. A Swedish registry study reported hyperemesis to be associated with congenital hip dysplasia, undescended testes and Down's syndrome (32). Others have found hyperemesis to be related to central nervous system malformations and an increased risk of congenital talipes equinovarus (31, 81). Contrary to these findings, severe nausea and vomiting in pregnancy has been associated with a protective effect on congenital heart defects in general, non-syndromic orofacial clefts and some other anomalies (82-84).

Child health

Undernutrition in utero may lead to persistent changes in blood pressure, cholesterol metabolism, insulin response and immune functions (85, 86). Such changes may contribute to disease in later life. However, no studies have related hyperemesis-induced malnutrition to later health of the child. Recent studies on prenatal growth suggest that early life experiences may influence the risk of specific cancers (87). Maternal hyperemesis is associated with hormone sensitive cancers in offspring, such as testicular cancer, and leukemia (88-95).

1.6. Socio-economic consequences

Most studies on economic consequences are focused on consequences of nausea and vomiting in pregnancy, although some have estimated the cost based on hospitalization which most probably includes severe forms of hyperemesis. Two Swedish studies reported that 12-14% of the patients found ordinary work during pregnancy impossible due to nausea and vomiting (96, 97). In Canada, 83% reported nausea and vomiting in pregnancy to affect their ability to perform daily activities (50). Similar findings have been described in studies from England and North America (13, 33, 98). The financial burden of severe nausea and vomiting in pregnancy is substantial (99, 100). The extra medical cost that children with low birth weight or preterm birth might induce has not been included in the estimates (70, 75).

1.7. Pathogenesis

Immunological changes

How the fetus manages to resist a cell-mediated immune response and rejection from the maternal immune system is still an enigma (101). To protect the fetus, changes in the humoral and cell-mediated immune systems are known to occur. Nevertheless, whereas starvation is associated with suppression of the immune system, hyperemesis is associated with a stimulation of the immune system (101-107). An overactivation of the immune system due to sympatic nerve activation has been observed, as well as a shift from Th1 helper cells towards Th2 helper cells (102, 108). Also, increased concentrations of fetal DNA in plasma of hyperemesis patients have been found in several studies (105, 107, 109). The fetal DNA is considered to be a result of damaged trophoblast cells at the feto-maternal interface, and is known to correlate with severity of the disease (105). The fetal DNA and the shift of T helper cells are both associated with autoimmune disease in later life (66, 109).

Human Chorionic Gonadotropin (hCG)

A review of 15 studies, all published between 1990 and 2005, explored the relation between hyperemesis and circulating hCG levels. In eleven studies, patients with hyperemesis had significantly higher levels of hCG (29). The level of hCG is reported to be associated with the severity of disease (110). It is hypothesized that hCG causes more severe hyperemesis by influencing the upper gastrointestinal tract, or by stimulating the thyroid function, since hCG

has structural similarity to thyroid stimulating hormone (TSH) (29). However, a variety of assay methods with different abilities to detect hCG subunits or hCG isoforms have been used in these studies. Hyperemesis has been found to be associated with the acidic half of hCG isoforms as well as hCG containing asialo-carbohydrate chains (25, 111, 112). Genetically determined differences in the production of hCG isoforms have also been suggested to explain the increased risk of hyperemesis in women of Indian and Pakistani origin in the UK (113). Moreover, hCG is currently considered to be a group of molecules, each with different functions, rather than one hormone (114).

Thyroid hormones

Gestational transient thyrotoxicosis (GTT) has previously been observed in up to two thirds of patients with hyperemesis, and has also been associated with the severity of hyperemesis (115). The thyroid function is known to vary during gestation, and is stimulated physiologically during early pregnancy (116, 117). HCG and thyroid stimulating hormone (TSH) are negatively correlated (116). TSH is suppressed during the 11^{th} to the 18^{th} gestational weeks, and hCG is considered to be primarily responsible for stimulating the thyroid gland (118). Among 15 studies on the relation between hyperemesis and GTT, 11 showed significantly higher T4 levels in the hyperemesis group whereas 9 out of 13 showed significantly higher TSH levels (29). The high incidence of GTT in hyperemesis patients has previously also been explained by thyroid hormone receptors that are hypersensitive for hCG. One family with hypersensitive TSH receptors to hCG has been described (119).

Estrogen

Several studies have associated hyperemesis with higher estrogen levels (31, 32, 103, 120, 121). Three prospective cohort studies have found higher mean estrogen levels in hyperemesis patients, whereas another reported a trend towards higher estradiol levels (31, 115, 122, 123). In pregnancy, increased levels of estrogen are associated with plasma volume expansion and an increase in extracellular fluid space and total body water (124, 125). This shift is described to cause a change in pH that might lead to a manifestation of a latent Helicobacter pylori infection (124).

Estrogen has also been reported to cause slower intestinal transit time and gastric emptying, explaining the accumulation of fluid (124). Regarding intestinal transit time and gastric emptying in relation to hyperemesis, studies have shown diverging results (126, 127).

Progesterone

The corpus luteum has its highest hormonal activity during the first trimester. One study found hyperemesis to be associated with higher progesterone levels, other studies did not (103, 123, 128, 129). Patients undergoing in vitro fertilization (IVF) often have multiple corpora lutea due to ovarian stimulation. In addition, progesterone may be administered for luteal support. However, no association between IVF and hyperemesis has been found (29).

Leptin, adreno-cortical hormones and serotonin

Leptin is a hormone regulating metabolic efficiency and food intake, interacting with cortisol, insulin, thyroid hormones, hCG, estradiol and progesterone (130). Two case-control studies have found increased levels of leptin among hyperemesis patients (130, 131). Although hyperemesis has previously been associated with an adreno-cortical insufficiency, later research has shown conflicting results (132, 133). Central and peripheral serotonin receptors play important roles in the vomiting reflex arch, but no association between release of serotonin and hyperemesis has been observed (134).

Oxidative stress

Pregnancy is a physiological state with enhanced oxidative stress due to high metabolic turnover and elevated tissue oxygen requirements (135). Several studies have found hyperemesis to be associated with increased oxidative stress (135-138). One study found hyperemesis patients to have reduced level of the ubiquitous antioxidant gluthathione, suggesting that these patients are exposed to increased oxidative stress (136). Another found increased reactive oxygen species activity, reflected in a 55% higher malondialdehyde level, and decreased antioxidant status among hyperemesis patients (137). These results suggest that an imbalance between lipid peroxidation and the antioxidant system may contribute to the pathogenesis of the disease. An insufficiency of antioxidants among hyperemesis patients, such as vitamins C and E, could enhance lipid peroxidation (139).

Liver enzymes

Liver function abnormalities have been reported in as many as 50-60% of all hyperemesis patients (140, 141). Liver enzyme abnormalities are found to be associated with later onset of the condition, more severe ketonemia and hyperthyroidism. Additionally, such abnormalities are explained by hypovolemia, malnutrition and lactic acidosis, and have been considered to be the result of, rather than the cause of, hyperemesis (25, 142). Also, women who are heterozygous for fatty acid oxidation defects have been reported to develop hyperemesis (143).

Amylase

Twenty four per cent of women with hyperemesis are reported to have increased levels of amylase, which is considered to originate from the salivary gland rather than the pancreas (144). Ptyalism has been described to accompany hyperemesis in several publications (145-148).

2. Etiology

As mentioned previously, hyperemesis was for a long time considered to be a disorder caused by psychological distress, fear of childbirth or resentment of the pregnant state (19, 149). Although little research has been performed to discard these theories, hyperemesis is presently seen as a complex disorder where the relative importance of genetic and environmental factors remains unclear. However, some associations between potential etiological factors and hyperemesis have been found. Compared to many other pregnancy disorders and outcomes, the general impression is that few etiological theories of hyperemesis have been tested out rigorously.

2.1. Infection with Helicobacter pylori

It has previously been described how gastric pH may change during pregnancy secondary to an accumulation of fluid due to increased levels of steroid hormones (124). This may activate a latent infection with Helicobacter pylori (HP) which subsequently causes the clinical syndrome of hyperemesis (34, 150, 151). Furthermore, changes in humoral and cell-mediated

immunity during pregnancy may also increase the susceptibility to de novo infection with HP or reactivation of HP (152). On the other hand, excessive vomiting may in itself increase the risk of HP infection, in which case HP infection would be secondary to hyperemesis. A large number of case-control studies, where pregnant women with hyperemesis are cases and pregnant women without the disease are controls, have been executed to estimate the association to HP. A systematic review which included 14 case-control studies published between 1998 and 2006, concluded that there is an association between hyperemesis and HP reflected in an overall OR of 4.45 (95% CI: 2.31-8.54) (153). This finding is further supported by an even more recent, although partly overlapping, meta-analysis of 25 case-control studies published from 1966 to 2008, showing an overall OR of 3.32 (95% CI: 2.25-4.90) (34). The association between hyperemesis and HP has been reported to be stronger for women of African origin compared to women of non-African origin; aOR of 5.3 versus 1.7, respectively (154). However, it is still uncertain whether HP is a cause or a consequence of hyperemesis.

2.2. Maternal factors

Maternal age and primiparity

Several studies have shown hyperemesis to be associated with young maternal age, where women above 35 years of age had 50% lower risk of hyperemesis compared to women below 20 years (31, 32, 77, 97, 155, 156). However, young women are also more prone to experience postoperative and chemotherapy induced nausea and vomiting, which suggests a more general susceptibility of nausea and vomiting or simply a lower threshold of vomiting (1, 157). Also, primiparous women are reported to have an increased risk of hyperemesis with crude odd ratios varying from 1.07 to 1.6 (31, 32, 77). In one study, the association between primiparity and hyperemesis disappeared when maternal age was adjusted for (155). There are no speculations as to how maternal age, or primiparity, might be related to an increased risk other than higher levels of estrogen and hCG (31, 118).

Maternal body mass index

Maternal BMI is associated with the risk of hyperemesis, although different studies have shown conflicting results. A large study from Sweden reported that women with low pre-pregnant BMI had increased risk of developing hyperemesis, OR of 1.43 (95% CI: 1.33-1.54),

which is in line with some earlier studies (130, 158-160). However, Depue et al. observed the opposite, that increased BMI was a risk factor for hyperemesis, OR: 1.5 (31). No relationship between BMI and hyperemesis was reported in other studies (155, 161, 162). Inconsistencies between the findings may be explained by differences in study designs, sources of data and availability of information on potential confounders. Whereas women with high BMI are known to have higher levels of estrogen, low BMI is reported to be associated with high levels of hCG (31, 118). One of the main objectives in our current thesis was to investigate association of pre-pregnant BMI and hyperemesis.

Pre-pregnant conditions

A population based cohort from Canada reported hyperemesis to be associated with several pre-pregnant conditions, such as hyperthyroid disorder, psychiatric illness or gastrointestinal disorders (adjusted RR: 4.5, 4.1 and 2.5, respectively) (155). Possible explanatory mechanisms to these associations have been described previously in this thesis. It is currently not known what is the cause and what is the consequence of hyperemesis. To have asthma or diabetes was also associated with an increased risk, adjusted RR being 1.5 and 2.6, respectively. This study did not distinguish between different forms of diabetes, nor did it provide suggestion as to why women with diabetes might be more prone to develop hyperemesis. Regarding asthma, there is one study based on data from MBRN published in 1972, reporting asthma patients to have almost three times higher risk of hyperemesis compared to women without asthma, 2.1% versus 0.8%, respectively (163). This was explained by the possibility of a better registration of hyperemesis among asthma patients, by emotional reactions in both conditions and by hormonal changes in pregnancy related to fetal gender (163). Women with female fetuses are reported to have increased asthma symptoms during pregnancy (164).

2.3. Pregnancy-specific factors

Fetal gender

Women carrying a female fetus are more at risk of nausea and vomiting in pregnancy. This has been observed since Hippocrates (15, 156). Numerous studies have found hyperemesis to be associated with female fetuses (32, 121, 161, 165-169). The strength of this association has

been reported to correlate with the severity of the disease (156, 165). The risk of having a female fetus was reflected in an aOR of 1.08 (95% CI: 1.02-1.14) for nausea and vomiting in pregnancy, and an OR of 1.8 (95% CI: 1.5-2.0) for women who were hospitalized due to hyperemesis for more than three days. Two studies reported that female fetuses were associated with hyperemesis given that the symptoms occurred during the first trimester (166, 168). Another study found female fetus neither to be associated with the severity nor the time point of symptoms (169). There have been speculations as to whether the sex ratio between male and female fetuses among women with hyperemesis can be explained by a selective loss of male conceptions, the timing of intercourse or altered hormonal milieu at the time of conception, such as a low estrogen/gonadotrophin ratio (121, 168, 170). Increased levels of hCG or estrogen in early pregnancy are associated with female fetus as well as to trigger the development of hyperemesis (32, 171).

Multiple gestations

Several studies have found hyperemesis to be associated with multiple gestations (32, 76, 77, 155, 168). Basso and Olsen as well as Fell et al. showed that hyperemesis is associated with female fetus and twinning, where the presence of at least one female in the twin pair was associated with higher risks, OR: 2.37 (95% CI: 1.77-3.17) and 3.7 (95% CI: 2.1-6.6), respectively (155, 168). Basso and Olsen speculated whether this finding could be related previous research findings by Steier et al. (168). Female fetuses are associated with increased levels of hCG, in single as well as multiple gestation pregnancies, in addition to an increased maternal hCG/placental weight ratio (171).

Molar pregnancies

Hyperemesis is furthermore associated with previous and present molar pregnancies (155, 172). Twenty six percent of complete moles are reported to present hyperemesis as one symptom (172). The partial moles more commonly present signs of missed abortion including vaginal bleeding and small uterine size. Both conditions are associated with increased levels of regular hCG, although this is reported to be less prominent for partial moles (114).

Interval between pregnancies

The interval between pregnancies is reported to be associated with the risk of hyperemesis, provided that the first pregnancy was unaffected (173). Compared to having an interval between pregnancies of 1 to 5 years, less than one year interval reduced the risk by 70% (aOR: 0.32, 95% CI: 0.18-0.58) whereas more than 10 years interval increased the risk by almost 60% (aOR: 1.57, 95% CI: 1.30-1.89). This might reflect a protective immunological memory created during a first healthy pregnancy.

2.4. Lifestyles

Smoking habits

Several studies have consistently reported that maternal smoking reduces the risk of hyperemesis; smoking before and during pregnancy seems to reduce the risk by 30 to 40% (13, 31, 77, 97, 120, 155, 165). A study from China reported that paternal smoking increased the risk of hyperemesis, aOR: 2.6 (95% CI: 1.7-3.9) (71). Smokers are found to have lower levels of estrogen and hCG, and the protective effect of smoking on hyperemesis has been explained accordingly (118, 174, 175). However, smoking also protects against postoperative nausea and vomiting (157). This effect has been ascribed to the chemicals in cigarette smoke, which might have the ability to increase the livers' enzyme metabolism and thereby influence the effect of the medication used in anesthesia (157). In relation to nausea and vomiting in pregnancy, one could speculate if the same chemicals increase the metabolism of steroid hormones, and thereby reduced the risk. Another objective of this thesis was to estimate the association between pre-pregnant smoking habits and hyperemesis.

Pre-pregnant diet

There is only one study that has explored the pre-pregnant diet on the risk of hyperemesis (120). The authors reported hyperemesis to be associated with increased intake of saturated fat before pregnancy; aOR=5.4 (95% CI: 2.0-14.8) per 15 gram increase. Another publication that had focused on women's diet in relation nausea and vomiting in pregnancy, reported that societies that did not experience these symptoms in relation to pregnancy included more green vegetables in their diet (176).

Maternal education

Contrary to what has been previously reported, nausea and vomiting in pregnancy was found to be more frequent among women who were out of work or who worked at home, compared to those working outside home; OR: 2.86 (95% CI: 1.49-5.46) (13, 97). This is in line with another study, where women with more than 12 years of education had reduced risk of nausea and vomiting in pregnancy compared to those with less education (aOR: 0.74) (77). Furthermore, Helicobacter pylori infection is associated with low socio-economic status (SES) as well as hyperemesis (177). The effect of SES on the risk of hyperemesis has so far barely been studied.

2.5. Genetic factors

Women who had nausea and vomiting in their first pregnancy are more prone to have such symptoms in subsequent pregnancies (13, 77). Also, sisters of women with nausea and vomiting in pregnancy were at increased risk (13, 178). A study based on a Norwegian Twin Panel explored the contribution of maternal and fetal genetic factors to the variation in liability to nausea and vomiting in pregnancy. Using the classical twin study, comparing the correlation of liability towards nausea and vomiting in pregnancy in monozygotic and dizygotic twins, it was found that maternal genetic variation can explain about 50% of the population variance in this phenotype (179). The severity of nausea and vomiting seemed to be stable between pregnancies, and a change of partner did not seem to have any influence (180).

Regarding hyperemesis, a study based on data from women with two pregnancies as registered in the MBRN, showed that the risk of hyperemesis in a woman's second pregnancy is 15.2% if hyperemesis had occurred in the first, compared to only 0.7% if it had not occurred (173). A change in paternity reduced the risk of hyperemesis, which could imply that fetal genes contribute to the development of the disease. We are not aware of other studies on the familial aggregation of hyperemesis, except for an internet survey administered by the Hyperemesis Education and Research Foundation that reported a strong maternal influence on the risk of hyperemesis (181). Those estimates, however, may be biased upwards due to a potential overrepresentation of severely affected families. Also, there are no twin studies for hyperemesis, or other studies that estimate the overall heritability, or that test the influence of

fetal versus maternal genetic effects. In future studies of familial aggregation, the effects of environmental factors should be included in the interpretation.

2.6. Differences in occurrence between and within populations

Fairweather in his papers referred to several scientific journals from the 19th and 20th centuries that described ethnic differences in prevalence of hyperemesis (14). According to these publications, hyperemesis was more frequent in France, England and America than in Germany and Russia (16, 182, 183). Research from Hawaii, USA, Japan and Yugoslavia reported the prevalences to vary from 1.36% in Japan to 7.8% in Yugoslavia (16). Eskimos and native Africans were described to have low prevalence of hyperemesis (183). However, the validity of the data used in the variety of studies was questioned. Fairweather collected data from different centres in the UK, where the criteria for the diagnosis were relatively standardized. He found the prevalences of hyperemesis, even within the UK, to vary from 0.05% (Plymouth 1960-61) to 1% (Aberdeen 1956-60) (16). Likewise, a Swedish registry study reported a prevalence of 0.3% with considerable variability between different hospitals (32).

The cumulative incidence of severe vomiting in pregnancy in China was reported to be 10.8% (71). The prevalence of hyperemesis in Kuwait was 4.5% (184). In New Zealand, the prevalence of hyperemesis among Pacific islanders was found to be significantly higher compared to non-Pacific islanders and a control group from Wellington (185). In South Africa, severe nausea and vomiting was more frequent among white, Indian and colored, compared to black urban and black rural women, which is in line with two recent epidemiological studies on nausea and vomiting in pregnancy (10, 148, 156). In the USA, women with hyperemesis were more likely to be non-white (76). In Norway, immigrant women of with Pakistani or African origin have higher risk of developing hyperemesis compared to ethnic Norwegians (154, 186). One study investigating the influence of diet on nausea and vomiting in pregnancy, reported that women in 8 of 30 societies located in Asia, Africa, Oceania, North and South America, not experienced these symptoms (176). As mentioned above, differences in the definitions of hyperemesis, inclusion criteria and study designs may probably have influenced the results and complicated the comparison between

the studies. In order to better verify ethnic differences in prevalence of hyperemesis, there is a need of a universally agreed definition that can be used in large population based studies.

Studies on the occurrence of hyperemesis in different populations may give rise to new etiological hypotheses. Both environmental and genetic factors have been shown to explain differences in prevalence. Since migration is known to influence health over time, it may be particularly interesting to further study immigrant populations (187-195). If a group of people move from a high-prevalence country to a low-prevalence country, one would expect the immigrants to exhibit lower prevalence of the disorder as time passes if environmental and cultural factors are the main causes. A stable prevalence would suggest that genetic factors are of main importance, or that the causes are related to the possibility that immigrants adhere to traditions, including nutrition, of their home country. In addition to the study of migrant populations, ecological studies, where time trends or geographical variations in occurrence are related to the prevalence of specific environmental or genetic factors, can be informative. However, there are many methodological challenges related to an ecological study design, in particular the low ability to control for confounding factors.

In Norway, large population based health registries and nationwide, prospective birth cohorts are available for research. In the present thesis we have attempted to examine some specific research questions related to the etiology of hyperemesis by using these facilities.

3. Aims of the study

The aim of the thesis was to come closer to understanding the etiology of hyperemesis, by investigating the contribution of genetic and environmental factors to the development of hyperemesis. The long-term benefits of etiological understanding might be better preventive actions and early treatment.

The specific aims were:

- To estimate the prevalence of hyperemesis according to maternal country of birth. To explore if differences in occurrence of hyperemesis can be explained by maternal socio-economic factors (Paper I).
- To estimate the relative risk of hyperemesis among first generation immigrants in relation to their length of residence in Norway (Paper II).

- To estimate the relative risk of hyperemesis according to parental consanguinity (Paper III).
- To estimate the relative risk of hyperemesis according to pre-pregnant body mass index and maternal smoking habits (Paper IV).
- To estimate the recurrence risk of hyperemesis across generations according to whether the subjects under study themselves were born after pregnancies complicated with hyperemesis or not (Paper V).

4. Material and methods

4.1. Data sets

The Medical Birth Registry of Norway (MBRN)

The MBRN is a population based registry of all births in Norway, currently comprising more than 2.3 million births. It was established in 1967, after the Thalidomide tragedy, to survey and detect changes in perinatal health (196). Registration is compulsory by law. The attending midwife or physician fills in a standardised notification form including demographic data on the parents, maternal health before and during pregnancy and birth, complications and interventions during pregnancy and the conditions of the newborn (197). Notification of all live births, stillbirths and abortions from the 16th gestational week (1967-1998), or from the 12th gestational week (from 1999 and onwards) is reported one week after delivery.

The Norwegian Mother and Child Cohort Study (MoBa)

MoBa is a nationwide pregnancy cohort that includes about 107 000 pregnancies among approximately 91 000 women. Parents and children are followed in order to study causes of diseases. From 1999 to 2008 pregnant women were recruited to the study through a postal invitation after they had signed up for the routine ultrasound examination in their local hospital. The participation rate was 43.5% (198). The mother received three questionnaires during pregnancy. In the first questionnaire (Q1), received between 13 and 17 weeks of pregnancy, background factors, exposures and health variables were included (199). A second questionnaire (Q2) was sent out at approximately the 22nd week of gestation and asked for information on diet and cost supplements. In the third questionnaire (Q3), received at about 30 weeks of pregnancy, health status and new exposures during pregnancy were included. All

hyperemesis cases in MoBa had been hospitalized due to hyperemesis prior to the 25th week of gestation.

Data sets from Statistics Norway

Country of birth

Information on country of birth and maternal educational level was obtained from Statistics Norway's country of birth file and census data. The country of birth file was established by Statistics Norway in 1988 and provides the basis for analyses of the immigrant population (200). The information is recorded at the time of immigration to Norway, and then reported to the Central Population Registry. Statistics Norway considers the information on country of birth to have almost 100% reliable.

Education

Information on maternal educational level was obtained from the National Education Registry in Statistics Norway, covering all inhabitants of Norway. Educational level was recorded according to the Norwegian Standard Classification of Education with a separate code for the highest numbers of years completed. However, the educational level of immigrants was obtained only if they had been educated in Norway (201).

4.2. Design, samples and main variables

The target population is all pregnant women at risk of hyperemesis. The sampling frames are either births registered in the MBRN from 1967 to 2006 or pregnancies registered in MoBa for the period 1999-2008. The actual study samples in each paper after exclusions depend on the research questions.

Table 1 Overview of study populations and variables in Papers I- V

	Paper I	Paper II	Paper III	Paper IV	Paper V
Data source					
MBRN	+	+	+		+
Statistics Norway	+	+	+		
MoBa				+	
Number of births	900 074	50 904	806 665	33 467	544 087*
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cohort	Cohort
Outcome variable					
Hyperemesis gravidarum	+	+	+	+	+
Main exposure					
Maternal country of birth	+	+			
Length of residence		+			
Consanguinity			+		
Smoking habits				+	
Body mass index				+	
Maternal hyperemesis					+
Year of birth					
1967-2005	+	+	+		
1967-2006					+
1999-2008				+	
Parity					
P 0	+	+	+	+	+
P +		+			+
Plurality					
Singleton	+	+	+	+	+
Plural	+	+			
Covariates					
Maternal education	+	+	+	+	
Maternal age	+	+	+	+	+
Marital status	+	+	+		+
Sex of the fetus	+	+	+		+
Year of birth	+	+	+		+

* Parent and child

Classification of hyperemesis

Papers I, II, III, V:

Hyperemesis gravidarum in the MBRN was classified according to ICD 8 (1967-1998) and ICD 10 (1999-2005):

ICD 8

- 638.0- hyperemesis gravidarum with neuritis
- 638.9- hyperemesis gravidarum without mention of neuritis
- 784.1- nausea and vomiting – symptoms related to the upper abdominal tract[1]

ICD 10

- O 21.0- mild hyperemesis
- O 21.1- hyperemesis with metabolic disturbances
- O 21.9- vomiting in pregnancy, unspecified

Paper IV:

Hyperemesis gravidarum in MoBa (1999-2008):

- Prolonged nausea and vomiting in pregnancy that required hospitalization prior to the 25th gestational week.

4.3. Statistical analyses

Prevalences and cumulative incidences

It is common to denote proportions of specific disorders as they are notified in birth registries at birth as prevalences. If the pregnancies were followed from conception to end of the period when the disease can appear, around 22nd gestational week, the proportion that developed the disease should be called cumulative incidences. In the present situation, births are only notified if the pregnancy lasts beyond a certain gestational week in the first or second trimester. Thus, we do not have the ideal situation to estimate cumulative risks, which would

[1] Not included in Paper V

give the best estimate of the absolute risk of hyperemesis. The prevalence that we observe can be seen as an approximation to the absolute risk.

Relative risks

We have used multivariable logistic regressions to estimate odds ratios (Papers I, III, IV, V). Since hyperemesis is a rare disease, these odds ratios are good approximations to relative risk which is the risk of hyperemesis in an exposed group divided by the risk of hyperemesis in an unexposed group. We have included other variables in the regression models to control for confounding, and we have performed stratified analyses to assess both confounding and effect modification.

In Paper II, the relative risk of hyperemesis in relation to the length of residence in Norway was explored separately for each immigrant group. Because the same woman may have been included in the analyses more than once, generalised estimating equations (GEE) was applied to account for possible dependencies in the sample. The trends of prevalences of hyperemesis according to the length of residence in Norway were studied by applying time as a continuous variable in a linear logistic regression model.

All analyses were performed by SPSS 14 or 16 (SPSS Inc, IL, Chicago, USA), except for GEE where STATA software version 8 (STATA Corporation TX) was used.

5. Results

5.1. Summary of papers

Paper I: Variations in prevalence of hyperemesis gravidarum by country of birth: A study of 900 074 pregnancies in Norway, 1967-2005

Objective: To estimate the prevalence of hyperemesis in women living in Norway by their country of birth, and explore whether the variations in the occurrence of hyperemesis could be explained by differences in maternal socio-demographic factors.

Material and methods: The sample comprised all primiparous women registered in the Medical Birth Registry of Norway (MBRN) from 1967 through June 2005 (N = 900 074). Independent associations between country of birth and hyperemesis were studied by multiple logistic regressions with and without adjustment for potential confounders.

Results: The overall prevalence of hyperemesis in primiparous women in Norway during the study period was 0.89% (95% CI: 0.88-0.92). Women born in Western Europe had the lowest prevalence of hyperemesis (0.8%), whereas those born in India and Sri Lanka had the highest (3.2%). Women born in Africa (except for Northern Africa) and India or Sri Lanka were 3.4 (95% CI: 2.7-3.5) and 3.3 (95% CI: 2.6-3.4) times more likely to develop hyperemesis than women born in Norway, after adjustment for potential confounders.

Conclusion: Substantial variations in the prevalence of hyperemesis in Norway by country of birth could not be explained by the differences in maternal socio-demographic factors.

Paper II: Length of residence and risk of developing hyperemesis gravidarum among first generation immigrants to Norway

Objective: To estimate the risk of hyperemesis among first generation immigrants to Norway by length of residence.

Material and methods: The sample consisted of first generation immigrants with a prevalence of hyperemesis exceeding that of ethnic Norwegians by 50%, as registered in the Medical Birth Registry of Norway. The women were born in Turkey, the Middle East, North Africa, Other Africa, Iran, Pakistan, India and Sri Lanka and Central and South America, counting altogether 50 904 women. Independent associations were studied for each immigrant group by adjustment for potential confounders. To account for dependencies in the sample, generalized estimating equations (GEE) were applied.

Results: For women from Central and South America, adjusted analysis showed a decrease in risk of hyperemesis by longer residency (p value for trend = 0.026). Women born in Turkey who had been living in Norway for 6-8 years had a higher risk of hyperemesis than

newcomers, although no trend was observed over time (adjusted RR = 2.06, 95% CI: 1.06-4.02).

Conclusion: Associations between hyperemesis and duration of residence in Norway did not show any universal pattern across immigrant groups. Women born in Central and South America had a lower risk of hyperemesis with increasing length of residence. Some evidence of the opposite was found for women born in Iran, North Africa and Turkey.

Paper III: Consanguinity and the risk of hyperemesis gravidarum in Norway

Objective: To investigate if consanguineous relations between parents will increase the risk of hyperemesis, due to increased risk of homozygosity in hyperemesis-associated alleles in a fetus. To examine whether ethnic variations in the occurrence of hyperemesis can be attributed to consanguinity.

Material and methods: The sample comprised all Norwegian, Pakistani and Turkish primiparous women with singleton pregnancies registered in the Norwegian Medical Birth Registry in 1967-2005. Multivariable logistic regression was used to study associations between the degrees of consanguinity between women and their partners and the prevalence of hyperemesis. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: The prevalence of hyperemesis was 0.9%, 2.2% and 1.9% in Norwegian, Pakistani and Turkish women, respectively. Both Norwegian (OR = 0.93, 95% CI: 0.42 - 2.09), Pakistani (OR = 1.08, 95% CI: 0.68 - 1.74) and Turkish (OR = 1.08, 95% CI: 0.44 - 2.67) women related to their partners as first cousins had similar risks of hyperemesis as non-related women after adjustment for potential confounders.

Conclusion: Consanguinity was not associated with hyperemesis. The differences in the occurrence of hyperemesis between Norwegian, Pakistani and Turkish women were not attributable to consanguinity.

Paper IV: Maternal body composition, smoking and hyperemesis gravidarum

Objective: To study associations between maternal pre-pregnant body mass index (BMI), smoking and hyperemesis.

Material and methods: The sample consisted of 33 467 primiparous women from the Norwegian Mother and Child Cohort Study. All associations were studied by multivariable logistic regression with adjustment for potential confounders.

Results: Among non-smokers, underweight (OR= 2.36, 95% CI: 1.43-3.88), overweight (OR= 1.34, 95% CI, 0.99-1.81) and obese (OR= 1.48, 95% CI: 1.00-2.20) women were more likely to develop hyperemesis than normal-weighted women. No associations were found among smokers. Women who smoked daily (OR= 0.44, 95% CI: 0.32-0.60) or occasionally (OR= 0.64, 95% CI: 0.44-0.93) had lower risk of hyperemesis than non-smokers. No effect of partner's smoking was observed.

Conclusion: Both low and high BMI were associated with hyperemesis, but only among non-smokers. Maternal pre-pregnant smoking reduced the risk of hyperemesis while the partner's smoking habit had no effect.

Paper V: The recurrence of hyperemesis gravidarum across generations

Objective: To estimate the recurrence risk of hyperemesis across generations according to whether the subjects under study were born after pregnancies complicated with hyperemesis or not.

Material and methods: Linked generational data from the Medical Birth Registry of Norway (1967-2006): 544 087 mother-offspring units and 399 777 father-offspring units.

Results: Daughters born after a pregnancy complicated with hyperemesis had almost three times higher risk of developing hyperemesis compared to women who were born after uncomplicated pregnancies (cOR= 2.91, 95% CI: 2.40-3.52). Sons who were born after a pregnancy complicated by hyperemesis did not have increased risk of fathering a pregnancy

with hyperemesis compared to men who were born after unaffected pregnancies (cOR= 1.04, 95% CI: 0.71-1.53). Daughters born after pregnancies not complicated with hyperemesis had increased risk when the mother had hyperemesis in a previous or later pregnancy, cOR= 2.70, 95% CI: 1.33-5.49 if hyperemesis had occurred in one of the mother's earlier pregnancies and cOR= 3.30, 95% CI: 1.35-8.08 if it had occurred in a later pregnancy. Neither adjustment for maternal age at childbirth and period of birth, nor restriction to female or male fetal gender or primiparity, influenced our estimates.

Conclusion: We found a three-fold increase in the risk of hyperemesis among daughters if the mother had ever experienced hyperemesis, whereas the sons did not have an increased risk of fathering a pregnancy with hyperemesis. The observed pattern of familial clustering suggests that hyperemesis is transmitted through mothers but not through fathers, implying that maternal genes, not fetal genes, are capable of triggering the disease. However, environmental influences along the maternal line can not be excluded as contributing factors to the development of hyperemesis.

5.2. Validity study of hyperemesis

Since the validity of hyperemesis in the MBRN had not been studied previously, we performed a comparison between the MBRN diagnosis and hospital records. In line with a previous study on hyperemesis using data from MBRN, we also included International Classification of Diagnoses (ICD) of nausea and vomiting that are less specific, such as 784.1 in ICD 8 and O21.9 in ICD 10 (173). We selected all women who delivered at Ullevål and Akershus University Hospital from January 1st 1970 to March 31st 1970, from April 1st 1986 to June 30th 1986, from July 1st 1997 to September 30th 1997 and from October 1st 2001 to December 31st 2001, and included all cases registered with hyperemesis in the MBRN during these time periods (n=47). As controls we randomly selected women who delivered during the same time periods at the same hospitals, but who were not registered with hyperemesis in MBRN (n=503). The study was performed by comparison of the data obtained from the MBRN to the hospital records of these women. Data on nausea and vomiting, weight loss, dehydration and ketonuria were obtained from the hospital records. In order to be registered with hyperemesis according to the hospital record, considered to be the gold standard, two of three criteria had to be present: weight loss, dehydration or ketonuria.

Because of the rather low sensitivity of 50% reported in Paper I, I wanted to explore if the data could provide further information on whether the women had mild or severe hyperemesis, and therefore reinvestigated the hospital records of all cases registered with hyperemesis in the MBRN. This time, pregnant women with at least one clinical symptom of hyperemesis, nausea or vomiting, were registered as cases.

Unfortunately, not all hospital records were available at this point. This resulted in slightly different numbers than reported in our first paper. Other possible sources of error in the validity study might have been the fact that some patients had a double set of hospital records of which only one was found, or that the patient had been admitted with hyperemesis to another hospital without our knowledge.

Table 2 Hyperemesis registered according to the MBRN and hospital records

	Hospital record +	Hospital record -	Total
MBRN +	26	21	47
MBRN -	5	498	503
Total	31	519	550

The results showed a sensitivity of 83.9 (95% CI: 70.7-91.1), specificity of 96.0% (95% CI: 94.2-97.7), a positive predictive value (PPV): 55. 3% (95% CI: 41.1-70.0) and a negative predictive value (NPV) of 95.9% (95% CI: 90.2-101.6). Among the 26 registered as cases according to the hospital records and the MBRN, 9 were admitted to hospital with excessive vomiting leading to weight loss and metabolic disturbances (data not shown).

These results reflected an acceptable validity of hyperemesis diagnosis in MBRN (202). Furthermore, our findings suggested a certain misclassification due to a relative high number of false positive cases. The likely result of this misclassification is that the reported associations are closer to the null value (relative risk of 1) than the real associations. This conclusion assumes that the misclassification is non-differential.

6. Discussion

6.1. Methodological considerations

Random errors

Random errors reflect fluctuations around a true value of a parameter, and might occur as a result of poor precision, sampling error or variability in measurement. In epidemiological studies, the primary way to increase the precision is to increase the sample size (203). The use of all births that have been registered in Norway since 1967, comprising more than 2.3 million births, and the use of a large nationwide birth cohort including 107 000 pregnancies reduce the risk of random error to a minimum. In our analysis based on immigrants (or "first generation immigrants" before October 15th 2008), the sample size was reduced. Using a small sample size was reflected in wide confidence intervals for the estimated relative risks and in the p-values for trend across duration of stay in Norway (Paper II).

Systematic errors

Selection bias

Selection bias in the MBRN

Since the MBRN contains information of all births in Norway since 1967, selection is not a problem for the ethnic Norwegian population. Immigrants to Norway are labor immigrants, asylum seekers, refugees or people who have been allowed permanent residence for family unification. This represents a selection compared to the total population in their home countries.

The occurrence of hyperemesis in the MBRN is in relation to births, and not to pregnancies. According to Wilcox et al., 31% of all pregnancies are lost before the 24th gestational week, and as many as 22% are not even clinically recognized (204). Since hyperemesis is associated with the occurrence of molar pregnancies, and inversely associated with early miscarriages and ectopic pregnancies, our way of relating hyperemesis to registries of births may have affected prevalence estimates. An underestimation of hyperemesis due to the exclusion of molar pregnancies might be partly counterbalanced by exclusion of miscarriages. Even so, an

exclusion of multiple gestations in Paper III and V could also be associated with an underestimation of hyperemesis.

Selection bias in the MoBa

A recent study on recruitment bias among 73 000 participants in the MoBa reported that women who were younger than 25 years, were smokers, who lived alone, who had more than 2 previous births or previous stillbirths were all underrepresented in the MoBa compared to the total birth population (205). Multivitamin and folic acid users were overrepresented among MoBa participants. The selection was found to have implications for prevalence studies, but was not considered to cause any validity problem regarding studies of exposure-outcome associations.

Moreover, in our study based on data from MoBa, only 6.2% reported not to have Norwegian as their mother tongue. This reflects an underrepresentation of immigrants due to the fact that immigrants and Norwegian-born to immigrant parents (or "second generation immigrants" before October 15th in 2008) are known to comprise 10.6% of Norway's population by 2009 (200). Since immigrants with Pakistani or African origin are known to have increased risk of hyperemesis when residing in Norway, the risk of hyperemesis estimated in the MoBa is perhaps lower than the true value in the total birth population. Furthermore, fewer young women and fewer smokers participate in the MoBa, which might influence the prevalence of hyperemesis in opposite directions. However, we do not expect this selection bias to influence our main results on exposure-outcome associations.

Additionally, all cases in the MoBa had been hospitalized due to hyperemesis. Since all inhabitants of Norway are entitled to free health care, selection bias due to socio-economic background in relation to hospital admissions is unlikely. According to one previous publication, women living alone are less likely to be hospitalized due to hyperemesis (167). They are also less likely to participate in MoBa. Again, this should not influence exposure-outcome associations.

Information bias

Information bias on hyperemesis in the MBRN

In the MBRN, hyperemesis was noted as a complication during pregnancy, and coded according to International Classification of Diseases, ICD 8 (1967-1998) and ICD 10 (1999-2005). The former director of MBRN, Lorentz Irgens, stated that ICD 9 was never used by the MBRN (personal communication). In his opinion this was due to ICD 9 not containing major changes compared to ICD 8, and because ICD 10 was to be introduced shortly after. The prevalence of hyperemesis in the MBRN according to ICD 8 was previously reported to be 0.8%, whereas the prevalence of hyperemesis among the first 24 000 included women in the MoBa (1999-2000) was 1.3% (173). The differences in prevalence were explained by the possibility of underreporting of hyperemesis in the MBRN or a change in prevalence of hyperemesis over time. Also a change in the diagnostic criteria of hyperemesis or reporting routines was mentioned as a possible source of error. In 1999, the notification form to MBRN was revised. For diseases like preeclampsia, not for hyperemesis, check boxes were introduced instead of written ICD diagnosis. The subsequent slight increase in prevalence of preeclampsia has later been explained by better reporting due to the use of checkboxes, which is in line with a quality study of the Swedish medical birth registry (206, 207). Results from our first paper showed a stable prevalence of hyperemesis of 1% from 1977 to 2005. This finding might reflect the unchanged reporting routines of hyperemesis; although the prevalence form 1967 to 1976 was found to be 0.7%, which implies the opposite, at least for that time period.

Until our validity study was conducted, the reliability of hyperemesis diagnosis, as registered in the MBRN, had not been investigated thoroughly. Supposed that the misclassification we found is not related to the exposures we have used, we expect that the effect of misclassification on odds ratios are towards the null value, which means that they are closer to 1 compared to the true value. The result of such misclassification is an underestimation of the associations.

Information bias on hyperemesis in the MoBa

In the MoBa, women registered with hyperemesis reported during their 30th week of gestation if they had been admitted to hospital due to prolonged vomiting and nausea prior to the 25th week of gestation during their actual pregnancy. Unfortunately, we had no data on exact time for hospitalization, but further analysis showed that 74% of the women we studied were admitted before the 13th gestational week (data not shown).

We performed a validity study of the hyperemesis diagnosis in two different hospital registries in time periods that only partly overlapped the MoBa (data not shown). Even so, we consider the diagnosis for severe hyperemesis used for women admitted to Norwegian hospitals to have been and probably still to be valid.

Information bias in the explanatory variables

- Country of birth and length of residence

Country of birth was exclusively related to maternal country of birth in Papers I, II and III. As previously mentioned, the country of birth file was established by Statistics Norway in 1988 and provides the basis for statistical analyses for the immigrant population (200). The information is recorded at the time of immigration to Norway, and then reported to the Central Population Registry. Statistics Norway considers the information on country of birth to be of almost 100% reliable. However, the immigrant population was categorized according to countries that were culturally and geographically related. This is an item for further discussion since such classification may influence our estimates. Information bias on the length of residence in Norway is highly unlikely as it was calculated by using information on the data on immigration from Statistics Norway where information on the date of immigration is registered.

- Pre-pregnant BMI

Pre-pregnant BMI was calculated using data obtained from the first questionnaire received in the MoBa (Q1). This information was supported by the woman's antenatal card that she always carries with her during pregnancy. It contains information on her height and pre-pregnant weight as registered during the first consultation in pregnancy. Anyhow, information bias on BMI is thoroughly addressed in Paper III.

- Pre-pregnant smoking habits

Pre-pregnant smoking habits and the partners' smoking habits were both reported in Q1. Even though smokers are known to report their smoking habits inaccurately, the information given is considered acceptable for large epidemiological studies (208). Additionally, Norwegians seem to report their smoking habits correctly (209). The interpretation of our data on smoking habits is discussed in Paper IV.

- Education

In the MBRN, information on maternal education level was obtained from the National Education Registry in Statistics Norway, covering all inhabitants of Norway. Education level was recorded to the Norwegian Standard Classification of Education with a separate code for highest numbers of years completed. However, exact information on educational levels for immigrants is difficult to obtain unless they have been educated in Norway. The response rate is low, particularly when coming from immigrants with low educational levels (210). Missing data on education do to some degree jeopardize education level as proxy indicator for socio-economic conditions. In the MoBa, however, education was thoroughly registered, and highest education completed was used in our study (199). In our study population, 2.6% had missing information on education.

Confounding

For a variable to be a confounder, it must be associated with the outcome and be unevenly distributed over the exposure or disease categories (211). Because our data sets are based on large random samples, an uneven distribution of the confounder by chance is not very likely. In our study, confounding was controlled for by entering variables of interest into logistic regression models or by use of stratified analyses. Residual confounding by variables that have not been measured, such as infections, nutrition and other unknown environmental factors influencing the risk of hyperemesis, cannot be excluded.

Advantages and limitations

The obvious advantage of our study is the use of a population based birth registry and a nationwide, large cohort. The validity of hyperemesis in the MBRN was tested and found acceptable. Additionally, the MBRN comprises several generations, providing data for studies

on intergenerational recurrence risks. Furthermore, Statistics Norway provided an excellent overview of immigrants to Norway, both in regards of country of birth, date of immigration and the infants' biological father.

In the MoBa there was an opportunity to distinguish between nausea and vomiting in pregnancy and hyperemesis, and to investigate risk factors in relation to the development of severity of the disease. In the MBRN, however, there might have been a gradual transition between nausea and vomiting in pregnancy and hyperemesis, registered as hyperemesis, in addition to a certain degree of misclassification which is previously addressed.

Finally, as previously discussed, the high proportion of missing information on education among immigrants has been of some concern.

6.2. Interpretation of results and comparison with others

The effect of maternal country of birth

Since genetic aspects will be discussed thoroughly in relation to another main finding, we will here focus on possible environmental factors that might contribute to explain ethnic differences in occurrence of hyperemesis.

The prevalence of hyperemesis is known to vary between populations and subpopulations and has been described earlier in this thesis. These differences in prevalence can be explained by variations in study designs, different diagnostic criteria for hyperemesis or differences in how ethnic groups have been categorized. But ethnic differences can also be caused by environmental or genetic factors not yet explored. Our findings, however, confirm what smaller Norwegian case-control studies earlier have reported, that women of Pakistani or African origin have higher risk of hyperemesis compared to ethnic Norwegians (154, 161, 186). Furthermore, our study adds new knowledge in terms of showing differences in risk of hyperemesis between numerous, well-defined immigrant groups. Women born in India, Sri Lanka and Africa other than North Africa had the highest risk of hyperemesis compared to ethnic Norwegian women with an aOR of 3.28 and 3.35, respectively.

Norway has a relatively short history of immigration, compared to other countries (210). The ethnic differences in prevalence of hyperemesis observed could therefore be related to the migration itself or be explained by the heterogeneity of Norwegian immigrants. In June 2009, immigrants and those born in Norway to immigrant parents constituted 10.6% of Norway's population, whereby 38% were refugees with families and 33% came as labor immigrants or students (200). Loss of social network or position, increased psychological stress, changes in diet and exposure to new disease patterns are all factors that might play a role in triggering the development of hyperemesis (212, 213). Also underlying or concomitant medical conditions could contribute to hyperemesis (214-216). One study reported that African immigrants to Norway have increased risk of Helicobacter pylori infection, and that hyperemesis patients of African origin had a stronger association to HP than non Africans (154). How hyperemesis, HP and ethnicity are connected is currently not known. African women may be infected by a more aggressive variant of the bacterium (217, 218).

Since immigrants have often been associated with low social position in the receiving societies, we studied if ethnic differences in prevalence of hyperemesis could be explained by differences in socio-economic factors (219, 220). In our multivariate analyses we used maternal education level as proxy for socio-economic variables, and found that maternal education did not influence the risk of hyperemesis. Since some immigrant groups had a large proportion of missing information on maternal education, we performed additional analyses among ethnic Norwegians who had highly reliable information on education. The results showed that adjustment for maternal education did not change the risk of hyperemesis. However, the role of SES as a contributing factor to ethnic differences in prevalence of hyperemesis needs to be further investigated.

The effect of length of residence in Norway

In our study, the prevalence of hyperemesis among immigrants to Norway did not show any universal pattern of change over time. This could reflect that our study sample was too small, or the time interval studied too narrow to have an impact on the prevalence of hyperemesis. Nevertheless, the results could also be explained by the aforementioned heterogeneity of Norwegian immigrants or a varying degree of acculturation. Unfortunately, there are few studies addressing changes in perinatal outcomes among immigrants in relation to duration of stay in their host country (221). We localized one study on Mexican immigrant women to

USA, who had higher risk of low birth weight and preterm birth with increasing length of stay. The original beneficial status of Mexican immigrants, due to a positive selectivity, was described as "the healthy migrant effect", previously reported to characterize labor immigrants (222). In contrast, a recent systematic review of immigrant women to Europe showed that they were clearly disadvantaged regarding pregnancy outcomes (219). The results were explained by possible biological as well as social susceptibilities. This study, however, did neither distinguish between different immigrant groups nor ethnicities. Three countries were reported to have a "strong integration policy", and therefore had reduced risks of adverse pregnancy outcomes, among those Norway.

The effect of consanguinity

Norway is reported to be the only country in the world that registers the biological relation between parents on a routine basis (223). Forty percent of children born in Norway to immigrants of Pakistani origin had parents who were consanguineously related (224). There is one large population based study also using the MBRN that reported a high recurrence risk of hyperemesis between pregnancies and a reduced risk of hyperemesis by 40% by change of paternity (173). The latter finding suggested that fetal genes might play a role in the development of hyperemesis. Given that fetal genes had controlled the risk of hyperemesis, this risk would increase with increased homozygosity of alleles in a fetus, which is the case for consanguineous marriages (225). We are the first to study the effect of increased homozygosity on the risk of hyperemesis in consanguineous marriages. The results of our study clearly indicated that there is no association between parental consanguinity and hyperemesis, which implies that fetal recessive genes do not seem to play a major role in the development of hyperemesis. This finding, however, does not exclude other modes of heritance.

Recurrence risk across generations

Mode of heritance and familial clustering has to a little extent been studied in relation to hyperemesis. In studies described earlier, the trend is a strong maternal influence (13, 32, 77, 179-181). In order to further explore the contribution of fetal and maternal genes to the development of hyperemesis, we estimated recurrence risks across generations. The strong maternal pattern of inheritance of hyperemesis shown in our study suggests that maternal

genes, not fetal genes, are at work. However, the effect of long-term environmental conditions cannot be excluded as an explanatory mechanism of our findings. Such long-term environmental conditions might be related to previously described risk factors such as maternal age, education level, BMI, smoking habits and ethnicity or exposure to infections. All the mentioned factors might belong to the shared risk of mothers and daughters, and need to be further explored.

The effect of pre-pregnant BMI and pre-pregnant smoking

Although several studies have found BMI to be associated with risk of hyperemesis, our study is the first to show that pre-pregnant low BMI and high BMI increased the risk of hyperemesis (31, 130, 158-160). Different time points of measuring BMI and various diagnostic criteria of hyperemesis complicate comparison between our study and previous studies. Furthermore, stratified analyses suggested that the effect of pre-pregnant BMI on hyperemesis was only present among non-smokers. Adjustment for SES slightly reduced the risk of hyperemesis. The underlying mechanisms for the effect of body mass on hyperemesis are not known, although low and high BMI are also associated with hormonal alterations described in relation to hyperemesis (31, 118, 130, 226). A previous publication also suggested that women with a lean body composition got more attention and health care from the physicians resulting in hospitalisation (158).

Nevertheless, like many earlier studies, we found a protective effect of pre-pregnant smoking on the risk of hyperemesis (31, 97, 155, 165). Again, different diagnostic criteria and time points for smoking make it difficult to compare our study to others. Moreover, our results suggested that the effect of maternal smoking is not modified by paternal smoking. When we further adjusted for SES, the effect of pre-pregnant smoking on hyperemesis became stronger, which could be explained by an underlying biological effect. Since smoking also protects against nausea and vomiting not related to pregnancy, such as postoperative nausea and vomiting, there are reasons to assume that a biological effect is likely (157).

Another issue discussed in our study is if the mothers' avoidance of smoking in pregnancy is a consequence of hyperemesis. Among the 7 135 women who reported daily smoking prior to pregnancy, 4 266 reported to have quit smoking during pregnancy. Among these, 38.2% stopped during the first four weeks (early quitters). Given that late quitting lowers the risk of

hyperemesis more than early quitting, an important question would be if women would tend to stop smoking during pregnancy when experiencing nausea and vomiting. This complicates the interpretation of the association between smoking in pregnancy and hyperemesis. In a further analysis, we did find that the proportion of early quitters comprised 47% of women with hyperemesis and 38% of women without hyperemesis. In other words, hyperemesis may lead to an early abandonment of the smoking habit.

7. Conclusions and future research

The present thesis presents evidence of ethnic differences in the prevalence of hyperemesis. All immigrant women residing in Norway, except those born in Western Europe or North America, had increased risk of hyperemesis compared to ethnic Norwegians. The ethnic differences could not be explained by the socio-economic factors studied. Length of residence in Norway did influence the risk of developing hyperemesis, but did not show any universal pattern across the immigrants groups. Consanguinity did not influence the risk hyperemesis, which suggests that fetal recessive genes are not playing a major role in the development of hyperemesis. The study of familial clustering of hyperemesis showed a high intergenerational recurrence risk of hyperemesis which is transmitted through the mothers. This indicates that maternal, not fetal, genes are at work, although co-variation of environmental factors also might contribute to the development of hyperemesis. Finally, we showed that low as well as high BMI increased the risk of hyperemesis, at least among non-smokers. Smoking was found to protect against hyperemesis.

In order to explore causes and consequences of hyperemesis, there is need for a universally agreed definition of the condition. The use of previously described questionnaires, such as Pregnancy Unique-Quantification of Emesis (PUQE), provides a possibility to estimate the severity of symptoms and distinguish between nausea and vomiting in pregnancy and hyperemesis, enabling comparison of future research results. Moreover, such factors as ethnic differences and patterns of familial clustering might be fruitful starting points for further studies on causal inference of hyperemesis (227). Additionally, one would need to follow HP infections in women from the pre-pregnant state through the first trimester to understand the temporal relation between HP and hyperemesis. Furthermore, randomized clinical trials of HP eradication in women with hyperemesis would shed light on the causal connection. Such studies have not yet been published.

8. Ethical considerations and implications for health care providers

Bhopal has addressed the importance of paying extra attention to ethics and justice when focusing on ethnicity or race in health care and medical science (228). In the current thesis, general ethical principles have been applied according to the Helsinki Declaration (229). Regional Committees for Medical and Health Research Ethics, The Data Inspectorate and Norwegian Directorate for Health have approved the study. My intension with this thesis has been to do good.

This thesis showed that some groups of immigrant women are more prone to develop hyperemesis than ethnic Norwegian women, when residing in Norway. Hopefully, this knowledge can create a better awareness and care for pregnant women in general, and for immigrant women with in particular.

Furthermore, this thesis revealed that women with a family history of hyperemesis have an increased risk of developing hyperemesis. This new knowledge might be useful for pre-pregnancy counseling.

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I

II

III

IV

Abstract

Maternal body composition, smoking and hyperemesis gravidarum

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Objective: To study associations between maternal pre-pregnant body mass index (BMI), smoking and hyperemesis gravidarum (HG).

Study design: The sample consisted of 33,467 primiparous women from the Norwegian Mother and Child Cohort Study. Data on HG, BMI, education, maternal age, eating disorders maternal and paternal smoking were obtained from questionnaires. All associations were studied by multiple logistic regression.

Results: Among non-smokers, underweight (OR, 2.36; 95%CI, 1.43-3.88), overweight (OR, 1.34; 95%CI, 0.99-1.81) and obese (OR, 1.48; 95%CI, 1.00-2.20) women were more likely to develop HG than normal-weighted women. No associations were found among smokers. Women who smoked daily (OR, 0.44, 95% CI, 0.32-0.60) or occasionally (OR, 0.64; CI, 0.44-0.93) had lower risk of HG than non-smokers. No effect of partner's smoking was observed.

Conclusion: Both low and high BMI are associated with HG, but only among non-smokers. Maternal pre-pregnant smoking reduces the risk of HG while partner's smoking has no effect.

Keywords: Hyperemesis gravidarum, smoking, body mass index, socioeconomic status

INTRODUCTION

Hyperemesis gravidarum (hyperemesis) is a disease characterized by excessive nausea, vomiting, metabolic disturbances and weight loss in early pregnancy [1]. It is the most common reason for hospital admittance in early pregnancy among women with live births, and the second most common reason for hospitalisation in pregnancy [2;3]. Moreover, hyperemesis increases the risk of low birth weight and preterm delivery [4-10]. However, the etiology is unknown [11;12].

Recently, a large study from Sweden reported that women with low pre-pregnant body mass index (BMI, kg/m^2) had increased risk of developing hyperemesis [13]. Obesity was a protective factor. Although these findings are in line with earlier small scale retrospective [14] and prospective [15] studies, Depue et al [16] observed the opposite, that increased BMI was a risk factor for hyperemesis. No relationship between BMI and HG was found in relatively small Norwegian [17] and Japanese studies [18] or in a large Canadian study [19]. Inconsistencies between the findings may be explained by differences in study designs, sources of data and availability of information on potential confounders.

Contrary to the conflicting evidence on the associations between BMI and hyperemesis, several studies have consistently reported that maternal smoking reduces the risk of hyperemesis [16;19;20]. Given that both smoking habits and BMI is associated with social background, it is possible that the observed associations with hyperemesis may develop according to factors related to socioeconomic status [21]. In addition, effects of partner's smoking habits in relation to hyperemesis remain unexplored. A previous study from China reported that paternal smoking increased the risk of hyperemesis [5]. Although the associations

between BMI and hyperemesis in the Swedish study were adjusted for maternal education and smoking these findings have not been replicated in other settings.

The aim is to study whether the association between hyperemesis and pre-pregnant BMI is modified by maternal smoking habits, using a large Norwegian population-based pregnancy cohort.

MATERIALS AND METHODS

This study is a subproject of the Norwegian Mother and Child Cohort Study (MoBa). In brief, MoBa is a nation-wide pregnancy cohort that aims to include 100, 000 pregnancies, and follow parents and children for etiologic studies of disease. Pregnant women are recruited to the study through a postal invitation after they have signed up for the routine ultrasound examination in their local hospital. The participation rate is about 40% [22]. In the first questionnaire (Q1), received between 13 and 17 weeks of pregnancy, background factors, exposures and health variables are included. In the third questionnaire (Q3), received at about 30 weeks of pregnancy, health during pregnancy is included. The English translations of the questionnaires are available at http://www.fhi.no. Quality-assured data-files (version 4 released in 2008) were used. The study has been approved by the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate.

Only primiparous women who answered both Q1 and Q3 were included in the study. Altogether, 41,735 primiparous women answered Q1. Among them, 35,149 (84%) women also responded to Q3. After excluding women with missing data on main exposure variables (pre-pregnancy BMI and maternal smoking), 33,467 women remained in the sample.

Hyperemesis was defined as prolonged nausea and vomiting in pregnancy which required hospitalisation prior to the 25th week of pregnancy, as reported in Q3. The main exposure variables were pre-pregnant BMI and pre-pregnant smoking as reported in Q1 (categorized as shown in Table 1). Similarly to other studies from Nordic countries, the main variable used as a proxy for maternal socioeconomic status was the woman's length of education in years (Table 1), including a separate category for missing data. In addition, information on maternal age (coded as <20, 20-24, 25-29, 30-34, 35-39, and ≥40 years), eating disorders (categorized as yes and no) and the woman's report of her partner's smoking (categorized as yes and no) were obtained from Q1.

Associations between hyperemesis and maternal pre-pregnancy BMI and smoking were studied by multiple logistic regression. Crude and adjusted relative risks (RR) of hyperemesis for the main exposures were approximated by odds ratios (OR). Women with normal BMI (18.5-24.9 kg/m^2) and non-smokers were used as reference groups. All studied associations were adjusted for education, age, partners smoking and eating disorders. To study smoking as a modifying factor for the associations between hyperemesis and BMI, a test for interaction was performed in regression analysis. Moreover, regression analyses were repeated after the data were stratified by maternal smoking. In these analyses, occasional smokers and daily smokers were merged into one group. To study the effect of partner's smoking on hyperemesis as well as whether this effect can be modified by maternal smoking, four groups with all possible combinations of maternal and partner's smoking were created. The couples in which no one smoked were used as a reference group.

All analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL).

RESULTS

Altogether, 353 women reported having hyperemesis resulting in a prevalence of 1.1 % (95% CI, 1.0-1.2). The prevalence of hyperemesis by maternal education ranged from 0.7 % among women with the highest educational attainment to 1.7 % among women with the lowest. Moreover, women with the lowest education were more likely to be obese and more likely to smoke daily than the most educated women (Table 1).

Women with pre-pregnant BMI below 18.5 kg/m^2 had more than two times higher risk of developing hyperemesis compared to women with normal weight (cOR, 2.24; 95 % CI, 1.45-3.47). Overweight (cOR, 1.45; 95% CI, 1.13-1.87) and obese (cOR, 1.50; 95% CI, 1.06-2.12) women were also more likely to have hyperemesis than the reference group. These associations only slightly decreased after adjustment for all other studied factors, although the association between hyperemesis and obesity was reduced to non-significant level (Table 2).

In crude analysis, both occasional and daily smokers had about 30% lower risk of hyperemesis compared to non-smokers (Table 2). After adjustment for potential confounders, the risk of hyperemesis for daily smokers was more than 50% lower (aOR, 0.44; 95% CI, 0.32-0.60) while the risk among occasional smokers was almost 40% lower (aOR, 0.64; 95% CI, 0.44-0.93). The largest change in point estimates occurred after introduction of the partner's smoking into the models (data not shown).

Although the test for interaction between maternal pre-pregnant BMI and smoking was not significant (p=0.860), in stratified analysis, the effect of BMI on the risks of hyperemesis was limited only to non-smokers (Table 3).

Non-smoking women whose partners smoked were almost 40% more likely to report hyperemesis. Smoking women whose partners did not smoke were less likely to have hyperemesis compared to women from non-smoking couples (Table 4). After adjustment for maternal age, BMI, education and self-reported eating disorders, the association between partner's smoking and the risk of hyperemesis among non-smoking women disappeared. At the same time, maternal smoking was inversely associated with hyperemesis irrespective of whether the partner smoked (aOR, 0.59; 95% CI, 0.43-0.81) or did not smoke (aOR, 0.50; 95% CI, 0.34-0.73)

COMMENT

The results of the study suggest that underweight, overweight and obesity may increase the risk of HG. However, this association was observed among non-smoking women only. Maternal smoking before pregnancy was associated with lower risk of HG while partner's smoking did not influence either the risk of HG or the effect of maternal smoking.

The fact that the study is relatively large and the data on BMI and smoking habits were collected prior to the outcome, minimizes random error and to some extent systematic error. A recent study on self-selection and bias in MoBa concluded that differences due to self-selection might have implications for prevalence studies, but is most probably not influencing the validity of exposure-outcome associations [23]. Anyhow, the results have to be interpreted taking into account its potential limitations, such as self-report on data. However, as for HG, all participants were asked to report in a questionnaire set out during the 30th gestational week, whether they were admitted to hospital prior to the 25th week of gestation due to HG. The relatively short time interval between the hospitalisation and the reporting of HG to our study suggests that recall bias in relation to HG is unlikely. This can be indirectly supported

by the fact that the overall prevalence of HG in this study (1.1%) was comparable with the data results from neighbouring Sweden (1.0%) and from our previous study from Norway (0.9%)[13;24]. The differences may be attributed to the fact that the latter studies used the information from national birth registries. However, it is unknown whether self-reports overestimate the actual prevalence of HG or the registries underestimate it as was suggested in another Norwegian study [25].

Our main finding on increased risk of HG among women with low BMI is in line with several previous studies. In the largest to date Swedish study, women with BMI below 20 kg/m^2 had about 40% higher risk of HG than women with BMI between 20 and 24.9 kg/m^2 [13]. Matsuo et al reported a 60% increase in the risk of HG in Japan in women with BMI below 19.93 kg/m^2 [18]. In our study the association was even stronger, probably because we used the WHO cut-off for underweight (18.5 kg/m^2). Small studies from the USA and Turkey further support these findings [14;15], although the difference between methods used does not allow direct comparisons of the results. At the same time, our results suggest that overweight and obese women are also at increased risk of developing HG independently of other studied factors, contradicting the results of the Swedish study. Cedergren reported that overweight women had similar risk of developing HG as normal weighted women while obesity was found to be a protective factor [13]. An earlier study from Norway showed no association between mean BMI between groups with and without HG [17]. However, given that we observed a non-linear relationship between BMI on HG with both low and high BMI increasing the risk, it is possible that similar relationship was overlooked by using only mean values in the previous study. The findings by Depue et al, that BMI $\geq$ 24 kg/m^2 was associated with a 50% increased risk of HG, [16] have not been replicated before this study.

The use of different BMI categories or different diagnostic criteria of HG might explain the diverging results of previous research. We used self-reported data and our results may complement findings from previous studies where registry data were used [13]. Thus, the validity of the data on our main exposures, BMI and smoking has to be further discussed.

Previous studies have shown that self reported data on weight tends to be slightly underestimated and height overestimated resulting in underestimation of BMI [26]. In Norway, a standardised form is completed for all pregnant women at the first routine examination early in the first trimester of pregnancy. Measurements of height and pre-pregnancy weight are also recorded. Women were specifically advised in the instructions to the Q1 to use these records when filling in the questionnaire. Using this standardised form reduces the possibility for measurement bias of height and weight. The validity of other information obtained from questionnaires used in MoBa, particularly smoking, have been thoroughly discussed and it was concluded that pregnant women in Norway are unlikely to underreport their smoking [27;28].

Even if the estimates of both exposures and the outcome are likely to be valid, the overall validity of the study may be threatened if women have different probability of being hospitalised in relation to either BMI or smoking. Even though previously suggested [13], we do not think that women with HG with high or low pre-pregnancy BMI in Norway are more likely to be hospitalised than women with HG and normal pre-pregnancy weight. One may suspect, though, that strict anti-smoking hospital rules could make smoking women with HG avoid in-patient care. In order to explore this hypothesis, we used the same sample to analyze whether the smokers were less likely to be hospitalized for vaginal bleeding, which is another relatively common cause of hospitalization in early pregnancy. We found that this was not the

case, suggesting that our main findings are unlikely to be due to lower proneness of smokers to be hospitalized. Given that in-hospital care in Norway is free-of-charge, it is also unlikely that more socially disadvantaged women are less likely to be hospitalized. These points are supported by our experience from working in Norwegian hospital departments of obstetrics and gynaecology.

Smoking is previously not reported as an important etiological factor for HG, whereby the associations between smoking in pregnancy and HG have mainly been described as a side finding in studies with other hypotheses [16;17;19;20] . Results of a cohort study on risk factors of HG showed a protective effect of current smoking (OR= 0.6), which is very similar to our findings [19]. Smoking in early pregnancy has also been found to be associated with a lower occurrence of vomiting [29] or nausea and vomiting [30]. However, it is still unknown whether HG is the severe form of nausea and vomiting in pregnancy or another disease.

In order to study whether the observed effect of smoking is due to pre-pregnancy smoking only or due to both smoking before and during early pregnancy, we performed additional analyses of 1629 women who quitted smoking the first four weeks of pregnancy (early quitters) and 2637 women who quitted after the first month (late quitters). Both groups had lower risk of developing HG compared to women who did not smoke before pregnancy and the protective effect of smoking was more pronounced among late quitters (OR, 0.37; 95% CI, 0.23-0.61 vs. OR, 0.60; 95% CI, 0.36-1.01) suggesting that smoking both before and during pregnancy reduces the risk of HG.

Paternal smoking in relation to HG has barely been studied earlier. In a case-control study, Zhang and Cai observed that odds for partner's smoking were twice higher among cases than

among controls, however, they did not adjust for maternal smoking [5]. Our results, before they were adjusted for maternal smoking, also suggest an increased risk of HG among women whose partners smoke. Adjustment for maternal smoking reduces the association between HG and paternal smoking. Moreover, our results suggest that the effect of maternal smoking is not modified by paternal smoking.

Ethnic background is a strong confounder in studies on HG [24]. The prevalence of HG in non-Norwegian women is higher while the prevalence of smoking is lower than among ethnic Norwegians [31]. However, in MoBa only 6.2 % of the participants reported to have non-Norwegian mother tongue. Excluding these women from the analysis did not change the associations suggesting that our results are unlikely to be confounded by ethnicity.

Interestingly, in some previous studies, the associations between HG and other factors, for example, female gender, were only evident among women hospitalized during the first trimester[31;32]. In spite of the fact that the definition of HG used in this study includes the first 24 weeks of pregnancy, we additionally restricted the analysis to women who were hospitalized during the first 12 weeks. Altogether, 260 cases of HG (74%) occurred during the first trimester. With this restricted case definition, the results changed only marginally.

Why underweight or obese non smoking women have an increased risk of developing HG is uncertain. There has been some evidence that eating disorders are associated with an increased risk of HG [32-34]. However, pre-pregnant BMI was not explored as a confounding factor in these studies. Adjusting for eating disorders in our study did not change the association between pre-pregnant BMI and HG. Although confounding effects of somatic diseases which have been shown to be associated with HG [19] is beyond the scope of this

paper, we tested whether the most common of them, asthma, could influence the observed associations. Adjustment for maternal asthma did not change the results while analyses of other conditions, for example, diabetes, thyroid disorders, etc were not possible due to too few cases in this sample.

Publications which describe associations between pre-pregnant BMI, smoking and HG have explored HG from very different aspects [13-16;18-20;35;36]. The explanatory mechanisms for their findings are therefore diverging. Some studies reported that the metabolic features when having low BMI or having a marginal vitamin status might contribute to the development of HG [14;36]. Others explained their findings with altered endogenous hormone levels at the time of conception or to the extreme hormonal fluctuations which take place in pregnancy [14;15;18;20]. It has been suggested that underweight women who have low circulating estrogen prior to pregnancy might have an exaggerated response to the rise in estrogen during the first trimester [14]. Or that fat deposits in obese women neutralise placental factors which are thought to play a role in the development of HG [13]. Moreover, HG has been associated with high levels of estrogen, explaining why younger women, non-smokers and those with female fetuses have an increased risk of HG [16]. Another possible mechanism for the protective effect of smoking could be a reduced level of human chorionic gonadotropin (hCG), since increased levels of hCG are associated with hyperemesis [12], whereas a reduced level is reported among women who smoke during pregnancy [37].

Since there is no established biological pathway between smoking and HG or between BMI and HG, any suggestions of mechanisms would be speculative. The associations should be examined in others settings and, if replicated, further analyses should aim at explanatory proposed mechanisms, if possible, with analyzes of biological material.

In summary, not only underweight, but also overweight and obesity may increase the risk of HG while maternal smoking before pregnancy is associated with reduced risk. Moreover, the associations between maternal body composition and HG are apparent only among non-smokers. Paternal smoking neither influences the risk of HG itself nor modifies the effect of maternal smoking. The mechanisms that these effects are mediated through should be studied, as they may contribute to our understanding of this important, but relatively under-researched disorder.

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Table 1. Hyperemesis gravidarum (HG), pre-pregnant body mass index (BMI) and pre-pregnant smoking by length of education among primiparous women, The Norwegian Mother and Child Cohort Study, n=33,467

		Length of education (years)					
		≤12	12	13-16	≥17	Missing	Total
	Number of women	5,909	3,908	14,214	8,555	881	33,467
HG, %							
Yes	353	1.7	1.4	0.9	0.7	1.6	1.1
No	33,114	98.3	98.6	99.1	99.3	98.4	98.9
BMI (kg/m^2), %							
<18.5	1,156	4.8	4.0	2.9	3.0	5.0	3.5
18.5-24.9	22,623	57.9	62.0	68.4	75.4	68.4	67.6
25.0-29.9	6,779	23.3	22.4	20.7	16.6	18.4	20.3
≥30	2,909	14.0	11.5	7.9	5.0	8.2	8.7
Smoking, %							
No	22,542	48.7	56.6	71.6	78.7	61.4	67.4
Occasionally	3,790	9.6	10.8	12.0	11.8	10.1	11.3
Daily	7,135	41.7	32.6	16.4	9.6	28.5	21.3

Table 2. Absolute number of cases, prevalence and relative risks with confidence intervals (CI) of hyperemesis gravidarum (HG) by pre-pregnant BMI and smoking among primiparous women, The Norwegian Mother and Child Cohort Study, 1999-2008, n=33 467

	Number of women	Number of HG cases	Prevalence of HG, %	Crude OR*	95% CI	Adjusted OR†	95% CI
BMI (kg/m^2)							
<18.5	1,156	23	2.0	2.24	1.45 - 3.47	1.94	1.25 - 3.02
18.5-24.9	22,623	203	0.9	1.00	-	1.00	-
25.0-29.9	6,779	88	1.3	1.45	1.13 - 1.87	1.41	1.09 - 1.81
≥30	2,909	39	1.3	1.50	1.06 - 2.12	1.36	0.96 - 1.93
Smoking							
No	22,542	263	1.2	1.00		1.00	-
Occasionally	3,790	31	0.8	0.70	0.48 - 1.02	0.64	0.44 - 0.93
Daily	7,135	59	0.8	0.71	0.53 - 0.94	0.44	0.32 - 0.60

* OR: odds ratio

†Adjusted for maternal age, education, partners smoking and eating disorders.

Table 3. Absolute number of cases, prevalence and relative risks with confidence intervals (CI) of hyperemesis gravidarum (HG) by pre-pregnant body mass index (BMI) stratified by maternal smoking, The Norwegian Mother and Child Cohort Study, 1999-2008, n=33,467

	Number of women	Number of HG cases	Prevalence of HG, %	Crude OR*	95% CI	Adjusted OR†	95% CI
Non-smokers							
BMI (kg/m^2)							
<18.5	701	18	2.6	2.67	1.63 - 4.38	2.36	1.43 - 3.88
18.5-24.9	15,560	152	1.0	1.00	-	1.00	-
25.0-29.9	4,436	62	1.4	1.44	1.07 - 1.93	1.34	0.99 - 1.81
≥30	1,845	31	1.7	1.73	1.17 - 2.56	1.48	1.00 - 2.20
Smokers							
BMI (kg/m^2)							
<18.5	455	5	1.1	1.53	0.61 - 3.85	1.12	0.43 - 2.85
18.5-24.9	7,063	51	0.7	1.00	-	1.00	-
25.0-29.9	2,343	26	1.1	1.54	0.96 - 2.48	1.59	0.98 - 2.56
≥30	1,064	8	0.8	1.04	0.49 - 2.20	1.00	0.47 - 2.12

* OR: odds ratio, CI: confidence interval

† Adjusted for maternal age, education, partners smoking habit and eating disorders.

Table 4. Absolute number of cases, prevalence and relative risks with confidence intervals (CI) of hyperemesis gravidarum (HG) by own and partner's smoking among primiparous women, The Norwegian Mother and Child Cohort Study, 1999-2008, n=33,299*

Own	Partner	Number of women	Number of HG cases	Prevalence of HG, %	Crude OR	95% CI	Adjusted OR†	95% CI
No	No	18,231	197	1.1	1.00	-	1.00	-
No	Yes	4,200	63	1.5	1.39	1.05 - 1.86	1.15	0.86 - 1.54
Yes	No	4,940	33	0.7	0.62	0.43 - 0.89	0.50	0.34 - 0.73
Yes	Yes	5,928	57	1.0	0.89	0.66 - 1.20	0.59	0.43 - 0.81

OR: odds ratio

* 168 women had not reported on their partner's smoking habit

† Adjusted for BMI category, mother's age category, education and eating disorders.

The recurrence of hyperemesis gravidarum across generations

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ABSTRACT

Objective The aim is to estimate the recurrence risk of hyperemesis gravidarum (hyperemesis) across generations according to whether the daughters and sons under study were born after pregnancies complicated with hyperemesis or not

Design Population based cohort study

Setting Registry data from Norway

Participants Linked generational data from the medical birth registry of Norway (1967-2006): 544 087 mother-offspring units and 399 777 father-offspring units

Main outcome measure Hyperemesis in second generation

Results Daughters who were born after a pregnancy complicated with hyperemesis had almost three times higher risk of developing hyperemesis compared to women who were born after uncomplicated pregnancies (crude odds ratio 2.91, 95 % confidence interval 2.40 to 3.52). Sons who were born after a pregnancy complicated by hyperemesis did not have increased risk of fathering a pregnancy with hyperemesis compared to men who were born after unaffected pregnancies (1.04, 0.71 to 1.53). Daughters born after pregnancies not complicated with hyperemesis had increased risk when the mother had hyperemesis in a previous or later pregnancy (2.70, 1.33 to 5.49 if hyperemesis had occurred in one of the mother's earlier pregnancies and 3.30, 1.35 to 8.08 if it had occurred in a later pregnancy). Neither adjustment for maternal age at childbirth and period of birth, nor restriction to female or male fetal gender or primiparity, influenced our estimates.

Conclusions We found a three-fold increase in risk of hyperemesis among daughters if the mother had ever experienced hyperemesis, whereas the sons did not have an increased risk of fathering a pregnancy with hyperemesis. The observed pattern of familial clustering suggests that hyperemesis is transmitted through mothers but not through fathers, implying that maternal genes, not fetal genes, are capable of triggering the disease. However, environmental

influences along the maternal line can not be excluded as contributing factors to the development of hyperemesis.

INTRODUCTION

Hyperemesis gravidarum (hyperemesis) is defined as excessive nausea and vomiting in pregnancy starting before the 22nd week of gestation which might lead to nutritional deficiencies and weight loss [1;2]. It occurs in 0.5 to 2 % of pregnancies and is the most common cause of hospitalization in early pregnancy [3-6]. Hyperemesis is associated with adverse pregnancy outcomes such as low birth weight and preterm birth [7-9]. The etiology is unknown [3;4]. Previous research has to a little extent investigated how hyperemesis clusters in families. A study using the medical birth registry of Norway (MBRN) found that the risk of hyperemesis in a woman's second pregnancy was 15.2 % if hyperemesis had occurred in the first, compared to only 0.7 % if it had not occurred [10]. For women with hyperemesis in the first pregnancy, the risk of hyperemesis in the second pregnancy was 10.9 % after a change of partner, while it was 16.0 % if the partner remained the same [10]. This finding suggests that there might be a genetic liability to hyperemesis possibly involving both maternal and fetal genes, although environmental factors cannot be ruled out. The aim of this study is to extend our understanding of the etiology of this disease by estimating the risk of hyperemesis in daughters, and the risk of fathering a pregnancy complicated with hyperemesis in sons, depending on the presence of hyperemesis in their mothers. In addition, we want to estimate the risk of hyperemesis in daughters born after pregnancies not complicated with hyperemesis, but where their mothers had hyperemesis in a previous or later pregnancy.

METHODS

Population under study

The MBRN is a population-based, mandatory registry of all births in Norway, and contains data from 1967 to the present, providing an opportunity to study the occurrence of birth outcomes across generations [11-13]. The midwife or physician attending the birth fills in a

standardized form where demographic data on the parents, maternal health before and during pregnancy, complications and interventions during delivery and the condition of the newborn are described. After birth, a national identification number which is unique for each Norwegian inhabitant is provided by the population registry of Norway. We had access to records for the period 1967-2006, comprising 2.3 million births. We linked the identification numbers for single born children (male or female) in the older generation with identification numbers of mothers or fathers of single born children in the younger generation, including 544 087 mother-offspring pairs and 399 777 father-offspring pairs. The lower number of father-offspring pairs was mainly due to the older average age of fathers compared to mothers at the birth of their children and partly due to missing paternal data [7;8]. However, the father's identification number of the last generation was missing for 1.2 %.

Based on these data we estimated the recurrence risk of hyperemesis across generations according to whether the women and men under study were born after pregnancies complicated with hyperemesis or not (Figure 1). We also selected women in the older generation who had given birth to at least two daughters, where both daughters were registered with at least one pregnancy in the birth registry in the younger generation. We estimated the risk of hyperemesis dependent on the occurrence of maternal hyperemesis in another pregnancy than that leading to the woman under study. Mothers with recurrent hyperemesis were excluded. If the two maternal pregnancies are called M1 and M2 and the two pregnancies in the next generation are called C1 and C2, then M1, C1 and C2 were all primiparous births. We were interested in the risk of hyperemesis in C1 dependent on presence of hyperemesis in M2, and likewise the risk of hyperemesis in C2 conditional on the presence of hyperemesis in M1 (Figure 2).

Variables

The data on hyperemesis was obtained from MBRN using the ICD-8 (international classification of diseases, 8th version) codes: 638.0 and 638.9 employed in the period 1967 to 1998, and the ICD-10 codes: O 21.0, O 21.1 and O 21.9 for the period 1999 to 2006. Maternal age was categorized for both generations as < 20, 20-24, 25-29, 30-34 and 35 years or more. Parity was categorized as nullipara and para. The years of childbirth in both generations were categorized into 5-year periods.

Statistical analysis

The relative risks of hyperemesis were approximated by odds ratios, calculated from logistic regression using SPSS for Windows, version 16.0. Maternal age at birth and period of birth in both generations were considered possible confounders and adjusted for. Since female fetal gender is associated with increased risk of hyperemesis, we restricted analysis to female fetal gender in mother-daughter pairs and to male fetal gender mother-son pairs in order to avoid an overestimation or an underestimation of recurrence risk, respectively. Since primiparity is also known to be associated with an increased risk of hyperemesis, we repeated all analyses in primiparous women.

RESULTS

Mother-daughter recurrence

The children of the first generation (that belonged to 544 087 mother-daughter pairs) were born in the period 1967 to 1993, while the children in the second generation were born in 1981 to 2006. The mean year of birth for the two generations was 1972 and 2000, respectively. In the first generation, the prevalence of hyperemesis was 0.7 % (number of cases: 3 704), while in the second generation the prevalence was 1.1 % (number of cases: 5

791). If the mother had hyperemesis, the risk of hyperemesis in the daughter (recurrence risk) was 3.0 % while it was 1.1 % if the mother did not have hyperemesis, corresponding to a crude odds ratio of 2.9 (95 % CI: 2.4-3.5) (Table 1). An analysis of pairs where both mother and daughter were first born showed a slight increase in risk, whereas restriction to female fetuses did not influence the risk.

Mother-son recurrence

In the second cohort of 399 777 pairs, the children in the first generation were born during the period 1967 to 1990, and the prevalence of hyperemesis was 0.6 % (number of cases: 2 290). In the second generation the birth years were 1980 to 2006, and the prevalence was 1.1 % (number of cases: 4 526). If the mother had hyperemesis, the risk for the son of fathering a pregnancy complicated with hyperemesis was 1.2 %, while it was 1.1 % if she did not have hyperemesis (Table 2). The odds ratio was not significantly different from the null value with a crude odds ratio of 1.0 (95 % CI: 0.7 to 1.5). Restricting the sample to male fetuses or primiparous women did not influence our associations across generations.

Mother-daughter recurrence, when hyperemesis in the mother had occurred in another pregnancy

If the mother had hyperemesis in an earlier pregnancy (leading to an older sister of the woman under study), but not in the pregnancy in which the woman under study was a fetus, the risk of hyperemesis was 2.7 %, while it was 1.0 % if the mother did not have hyperemesis, corresponding to a crude odds ratio of 2.7 (95 % CI: 1.3-5.5) (Table 3). If the mother had hyperemesis in a later pregnancy (leading to a younger sister of the woman under study), the risk was 2.6 % contrasted to 0.8 % if the mother did not have hyperemesis; the crude odds ratio was 3.3 (95% CI: 1.4-8.1) (Table 3).

DISCUSSION

For daughters we found that the risk of hyperemesis was about three-fold elevated if their mothers had ever experienced hyperemesis in a pregnancy. This was regardless of whether hyperemesis had occurred in the pregnancy leading to the woman under study, or in whether hyperemesis occurred in a preceding or subsequent pregnancy. In contrast, men who were born after a pregnancy with hyperemesis did not have an increased risk of fathering a pregnancy complicated by it. We found that hyperemesis was being transmitted through mothers and not through fathers suggesting that it is maternal genes rather than fetal genes that contribute to the development of hyperemesis. However, although a large registry is used, the confidence intervals are relatively wide, and one can not exclude any influence of fetal genes based on these findings. One should also be open for an interpretation that the risk is not genetically transmitted, but is due to matrilineal co-variation of environmental factors.

Comparison with other studies

We are not aware of any other population studies of the recurrence of hyperemesis across generations. In a self-selected sample using an internet survey, a high degree of familial clustering of hyperemesis was reported [14]. A previous study on consanguinity and risk of hyperemesis in MBRN showed that consanguineous relations did not increase the risk, suggesting that fetal recessive genes are not playing a major role in the development of hyperemesis [15]. A study of recurrence of hyperemesis in successive pregnancies to the same woman showed that there was a lower recurrence of hyperemesis after a change of partner, suggesting that fetal genes may play a role [10]. However, lifestyles and socioeconomic conditions may well change along with a change of partner, and further studies should include more data on environmental factors.

Other studies have reported that siblings and mothers of women with nausea and vomiting in pregnancy are more likely to have the same symptoms [16-18]. Using the classical twin study, comparing the correlation of liability towards nausea and vomiting in pregnancy in monozygotic and dizygotic twins, it was found that that maternal genetic variation can explain about 50 % of the population variance in this phenotype[16]. The fact that hyperemesis is a rare disease occurring in a few percent of all pregnancies, whereas nausea and vomiting in pregnancy is very common occurring in up to 80 %, makes comparison between these studies and ours difficult [17]. Additionally, it is currently not clear how hyperemesis and nausea and vomiting in pregnancy are related [4].

Strengths and weaknesses

Our cohort is based on mandatory reporting during a period of 40 years, a standardized data collection comprising a whole population. This provides a reasonable level of precision and removes most selection bias. The validity of the data on hyperemesis in MBRN is acceptable and has been discussed in earlier publications [10;19]. We found the prevalence of hyperemesis to be higher in the second generation. This finding is in line with previous studies, and might be explained by better registration of hyperemesis in MBRN since 1999 or be due to an increased awareness of the condition [10;15;19]. When we adjusted for period of birth in both generations, the association across generations did not change.

In previous research, hyperemesis has been positively associated with young maternal age, primiparity, female fetal gender, low or high body mass index, non-smokers and Asian or African ethnicity [3;19-22]. In our study, however, the intergenerational recurrence risk of hyperemesis was not confounded by maternal age. Moreover, as we restricted the sample to

female fetuses when studying the recurrence risk between mothers and daughters and male fetuses when studying the mothers and sons, the results showed that the associations remained stable. This means that the intergenerational recurrence risk was not overestimated due to female fetuses or underestimated due to male fetuses. However, restriction to first born women in both generations slightly increased the recurrence risk of hyperemesis among mothers and daughters.

Unfortunately, variables such as body mass index, educational attainment and ethnic background were not available to us, and we could therefore not explore their possible confounding effects. Since most immigrants to Norway arrived after 1986, confounding by ethnicity in our data set is not very probable when studying recurrence risk across generations[19]. Even if body mass index and maternal education represent shared risk factors between mothers and daughters, it is highly unlikely that confounding of these factors could explain the intergenerational recurrence risk of hyperemesis within affected families. Nevertheless, information on smoking habits was available for the majority of women registered after 1998. A sub analysis showed that, regardless of the expected protective effect of smoking on the development of hyperemesis, additional adjustment for smoking slightly increased the intergenerational recurrence risk of hyperemesis (data not shown). Due to lacking information on smoking habits in the first generation and partly in the second generation, we were not able to study differences in intergenerational recurrence risk of hyperemesis among smokers and non-smokers.

Conclusions and implications for clinicians

Our results show a high intergenerational recurrence risk of hyperemesis which is solely transmitted through the mothers. Transmission of maternal genes as well as co-variation of environmental factors might contribute to the development of hyperemesis.

The results of this study might be of importance for future pre-pregnancy counseling.

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Table 1 Risk of hyperemesis and odds ratios (ORs) for hyperemesis with 95 % confidence intervals (CI) among daughters dependent on the occurrence of hyperemesis in the mother, MBRN 1967-2006.

	Hyperemesis in the mother	Number of pregnancies	Number of cases	Prevalence (%)	Crude OR	95 % CI	Adjusted* OR	95 % CI
All mother-daughter pairs								
	Yes	3 704	111	3.0	2.9	2.4-3.5	2.9	2.4-3.5
	No	540 383	5 680	1.1	1†		1†	
	Total	544 087	5 791	1.1				
Restriction to first birth order in both generations								
	Yes	934	30	3.2	3.2	2.2-4.6	3.2	2.2-4.7
	No	113 436	1 162	1.0	1†		1†	
	Total	114 370	1 192	1.0				
Restriction to female fetus								
	Yes	1 811	57	3.1	2.9	2.2-3.7	2.9	2.2-3.8
	No	262 345	2 942	1.1	1†		1†	
	Total	264 156	2 999	1.1				

*Adjusted for maternal age at childbirth, period of birth and parity (when not restricted to first birth order) in both generations
† Reference category

Table 2 Risk of fathering a pregnancy with hyperemesis and odds ratios (ORs) for hyperemesis (with 95 % confidence intervals (CI)) dependent on the occurrence of HG in the mother, MBRN 1967-2006.

	Hyperemesis in the mother	Number of pregnancies	Number of cases	Prevalence (%)	Crude OR	95 % CI	Adjusted* OR	95 % CI
All mother-son pairs								
	Yes	2 290	27	1.2	1.0	0.7-1.5	1.1	0.7-1.6
	No	397 487	4 499	1.1	1†		1†	
	Total	399 777	4 526	1.1				
Restriction to first birth order in both generations								
	Yes	569	7	1.2	1.2	0.6-2.4	1.2	0.6-2.5
	No	83 822	896	1.1	1†		1†	
	Total	84 391	903	1.1				
Restriction to male fetus								
	Yes	1 186	16	1.3	1.3	0.8-2.1	1.3	0.8-2.1
	No	204 319	2 183	1.1	1†		1†	
	Total	205 505	2 199	1.1				

*Adjusted for maternal age at childbirth, period of birth and parity (when not restricted to first birth order) in both generations
† Reference category

Table 3 Risk of hyperemesis and odds ratios (ORs) for hyperemesis (with 95 % confidence intervals (CI)) among sisters born after unaffected pregnancies, but where the mother had hyperemesis in previous or later pregnancy, MBRN 1967-2006.

	Hyperemesis in the mother	Number of pregnancies	Number of cases	Prevalence (%)	Crude OR	95 % CI	Adjusted* OR	95 % CI
Mother-daughter pairs *HG in an earlier pregnancy of the mother*								
	Yes	297	8	2.7	2.7	1.3-5.5	2.8	1.4-5.7
	No	42 209	428	1.0	1†		1†	
	Total	42 506	436	1.0				
Mother-daughter pairs *HG in a later pregnancy of the mother*								
	Yes	192	5	2.6	3.3	1.4-8.1	3.3	1.4-8.2
	No	42 209	339	0.8	1†		1†	
	Total	42 401	344	0.8				

* Adjusted for maternal age at childbirth and period of birth
† Reference category

What is already known on this topic

There is a high risk of recurrence in women who had hyperemesis in their first pregnancy

This risk is reduced by change of paternity, suggesting that fetal genes may contribute to the development of hyperemesis

Hyperemesis is not associated with consanguinity, implying that fetal recessive genes do not play a major role

What this study adds

We found that the recurrence risk of hyperemesis was about three-fold elevated among daughters if their mothers had ever experienced hyperemesis in a pregnancy

The recurrence risk of hyperemesis remained three-fold elevated was regardless of whether hyperemesis occurred in the pregnancy leading to the woman under study, or in whether hyperemesis occurred in a preceding or subsequent pregnancy

Men who were born after a pregnancy with hyperemesis did not have an increased risk of fathering a pregnancy complicated by it

The observed pattern of familial clustering suggests that hyperemesis is transmitted through mothers but not through fathers, implying that maternal genes, not fetal genes, are responsible for triggering the disease. However, effect of long term environmental influences along the maternal line can not be excluded as contributing factors to the development of hyperemesis

This study contributes with new knowledge that might be of importance for future pre-pregnancy counseling.

Figure 2. Risk of hyperemesis in older daughter (M1) or younger daughter (M2), both born after a pregnancies not complicated by HG.

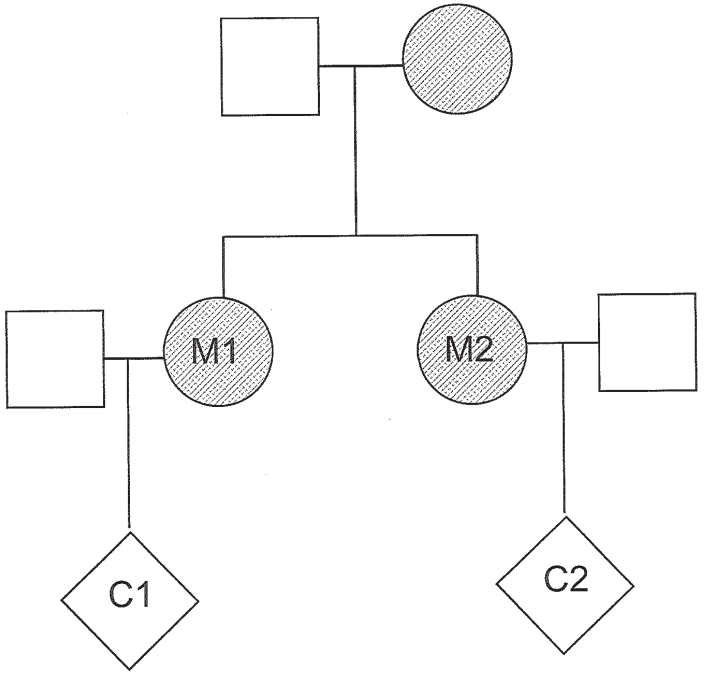

Figure 1. Risk of parenting a pregnancy complicated with hyperemesis for daughters and sons born after pregnancies with hyperemesis