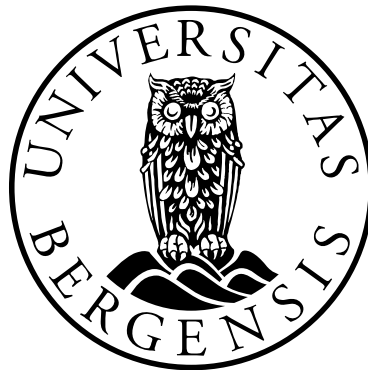# Treatment of nausea and vomiting during pregnancy

- with special focus on attitudes to and use of pharmacological treatment

Kristine Heitmann

Dissertation for the degree of philosophiae doctor (PhD)

at the University of Bergen

2016

Dissertation date: 25.05.2016

Year: 2016

Title: Treatment of nausea and vomiting during pregnancy

            - with special focus on attitudes to and use of pharmacological treatment

Author: Kristine Heitmann

Print: AiT Bjerch AS / University of Bergen

In loving memory of my dearest mother Ingrid Medby Heitmann

Scientific environment

This research project was carried out at the Research Group in Social Pharmacy, Department of Global Public Health and Primary Care and Centre for Pharmacy, University of Bergen. The work was financed by the Research Council of Norway (grant no. 195475).

Main supervisor:

Associate Professor Lone Holst, Department of Global Public Health and Primary Care and Centre for Pharmacy, University of Bergen.

Co-supervisor:

Professor Hedvig Nordeng, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo.

I have participated in the National PhD School of Pharmacy and attended PhD courses at the University of Bergen.

Acknowledgements

First and foremost, my heartfelt thanks to all the study participants who made this project possible.

I wish to express my sincere gratitude to my supervisors, Associate Professor Lone Holst and Professor Hedvig Nordeng. I am deeply grateful for all your help, guidance and support during this PhD-project. You're the best! I think you made an excellent "Team Supervisors", complementing each other perfectly. Lone, contributing to all papers, you have supervised the whole project. Your guidance was especially important with respect to the qualitative part of this project. Sharing office with you for over three years was very enjoyable. Thank you for always being available, and for all our discussions, also the non-work related. Hedvig, you have a remarkable enthusiasm for your research that has had a motivational effect on me, and your competence in pharmacoepidemiology and commitment to your work is unique. To both of you, thanks for letting me follow this NVP-path, even though this was not the original project idea. Also, a warm thank you for your patience, motivation, all our discussions, and all your comments and "red marks". I could never have done this without you!

I would like to thank my co-authors, PhD Angela Lupattelli, BA Caroline Maltepe and MScPharm Gro Cecilie Havnen, as well as my master students (that I shared with Lone). Angela, it has been an absolute pleasure to work with you. Caroline, I would like to express my gratitude for sharing your vast knowledge on management of nausea and vomiting during pregnancy. Gro, thank you for all our discussions and for sharing your clinical perspective. I am also very grateful for the excellent contributions from our master students, Hans Christian Svendsen, Ingvild Høva Sporsheim and Anja Solheimsnes, with whom two of the studies were carried out and results were discussed.

I wish to thank colleagues at the Centre for Pharmacy, for support and motivation, especially Professor Svein Haavik, who is a role model in Norwegian pharmacy, and

Foreword

My interest in drug use among pregnant women was born when I was doing my master's degree in social pharmacy and collected data at the maternity ward at Haukeland University Hospital. My master's project involved a survey of women who had recently given birth in which they were asked about their attitudes to and use of herbal medicines during pregnancy. During these interviews, it dawned on me how many pregnant women struggled with various pregnancy complaints and chronic illnesses that needed medical treatment, and how anxious these women were about using medicines during pregnancy. The result was that the conditions remained undertreated in many cases. At the same time, I also noted with great interest the more or less naïve attitude among many of the women towards herbal, *'natural'* medicines.

During my time working at a pharmacy after graduation, I further noticed that we received many enquiries from women suffering from nausea and vomiting during pregnancy (NVP). My impression from my encounters with these women was that, despite being ill, they were wary of using any medicines to relieve their symptoms. However, the majority tried both ginger and acupressure. Although my impression was that these treatments did not provide enough relief for many of the women, little more was done for them. They just 'hung in there'. This aroused my curiosity as to what *can* be done for these women, and how should NVP be managed? What is safe to use for NVP? What do we know about the effectiveness and safety of ginger use during pregnancy? How are women with NVP treated in general? How are Norwegian women treated compared to women from other countries?

Abbreviations

5HT	Serotonin
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body mass index
CAM	Complementary and alternative medicine
CI	Confidence interval
CTZ	Chemoreceptor trigger zone
D	Dopamine
EMA	European Medicines Agency
EPDS	Edinburgh Postnatal Depression Scale
EUROCAT	European Surveillance of Congenital Anomalies
FDA	U.S. Food and Drug Administration
GEE	Generalised Estimating Equation
GP	General practitioner
hCG	human Chorionic Gonadotropin
H. pylori	*Helicobacter pylori*
HG	Hyperemesis gravidarum
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision

LBW	Low birth weight
MBRN	Medical Birth Registry of Norway
MoBa	Mother and Child Cohort Study
NEL	Norwegian Electronic Medical Handbook
NGF	Norwegian Society of Obstetrics and Gynecology
NICE	National Institute for Health and Care Excellence
NVP	Nausea and vomiting during pregnancy
OR	Odds ratio
OTC	Over-the-counter
PUQE	24-hour Pregnancy-Unique Quantification of Emesis scale
Q1	Questionnaire 1 in MoBa
Q3	Questionnaire 3 in MoBa
Q4	Questionnaire 4 in MoBa
RCT	Randomised controlled trial
SGA	Small for gestational age
WHO	World Health Organization

Abstract

Background: Nausea and vomiting during pregnancy (NVP) is one of the most commonly experienced pregnancy complaints and has been associated with decreased quality of life and occupational and daily life functioning, as well as negative socioeconomic consequences. Though several treatment guidelines exist for NVP, including recommendations for medicines that are safe to use during pregnancy, we know little about how this condition is managed, both internationally and nationally in Norway. We also know little about attitudes to treatment of this complaint. Ginger is included in most guidelines. However, only one study exists that was designed to investigate the safety of its use during pregnancy.

Objectives: The main aim of this doctorial work was to explore various aspects of treatment of NVP. The specific objectives were: 1) to investigate whether exposure to ginger, a common NVP herbal drug, was associated with an increased risk of congenital malformations or other selected negative pregnancy outcomes; 2) to explore patterns of and factors related to NVP and its treatment across countries in Europe, North America, and Australia; 3) to explore thoughts and attitudes among Norwegian pregnant women and GPs about the treatment of NVP, and to identify potential barriers to optimal care for women with NVP; 4) to investigate the treatments used for NVP according to NVP severity among women in Norway, and to assess whether maternal characteristics and attitudes were related to the use of pharmacological treatment of NVP.

Methods: In order to address the above objectives, several methods and data sources were used. 1) The large population-based Norwegian Mother and Child Cohort study, which provides information on the use of ginger and several potential confounders, was linked to the Medical Birth Registry of Norway from which information on pregnancy outcomes was retrieved (Paper I). 2) The Multinational Medication Use in Pregnancy Study, a web-based cross-sectional study carried out among women and new mothers in 18 countries (Paper II). 3) Focus group discussions were used to explore thoughts about

and attitudes to the treatment of NVP among pregnant women and general practitioners (Paper III). 4) A web-based cross-sectional study was conducted among pregnant women and new mothers in Norway with NVP (Paper IV).

Results: The study in Paper I showed that the use of ginger during pregnancy was neither associated with any increased risk of congenital malformations nor with any increased risk of stillbirth/perinatal death, preterm birth, low birth weight, or low Apgar score.

In the study in Paper II, nausea during pregnancy was reported by 73.5% of women, 17.9% of whom used conventional medicines and 8.3% herbal medicines. The prevalence of self-reported nausea and its treatment varied across countries. Education, working status and folic acid use were significantly associated with the use of conventional medicines against nausea. Respondents who suffered from nausea also had a high burden of comorbidity.

In the focus group study in Paper III, the GPs thought it was important to normalise NVP symptoms. However, the women felt that their distress due to NVP was trivialised by the GPs. The women were sceptical about using medicines while pregnant, and avoidance was sought despite being ill. The GPs, who appeared to be uncertain and rather restrictive with respect to medical treatment of NVP, seemed to regard sick leave as an important part of the treatment regime. The women had good experience of graded sick leave.

The Norwegian study described in Paper IV showed that, of the 712 women who were included in the study, 8.7%, 61.7% and 29.5% had mild, moderate and severe NVP, respectively. A total of 38.9% women had used one or more antiemetics, of which meclizine was the most commonly used, closely followed by metoclopramide. Different drug utilisation patterns were found between the groups of women with mild, moderate and severe NVP, and many women with moderate and severe NVP had not used medicines for NVP (70.2% and 32.9%, respectively). Sick leave was prescribed without initiating medical treatment in the case of 62.1% of the women who had been on sick

leave. The women's beliefs about medicines had an important impact on their use of medicines for NVP.

Conclusion and implications: The findings of this doctorial work show that there are potential areas for improvement with respect to the management of NVP. The findings indicate 1) a need to increase awareness among healthcare personnel of the great distress women suffering from NVP may experience, and 2) that it is necessary to educate them about the recommendations in guidelines for the treatment of NVP. Due to the pregnant women's fear of teratogenic effects of medicines, balanced evidence-based information about the maternal and foetal risks of medicines for NVP and tailored risk communication are necessary in order to reassure pregnant women in need of NVP medication.

List of publications

I: Heitmann K, Nordeng H, Holst L (2013) Safety of ginger use in pregnancy: results from a large population-based cohort study. European Journal of Clinical Pharmacology 69 (2):269-277. doi:10.1007/s00228-012-1331-5

II: Heitmann K, Holst L, Lupattelli A, Maltepe C, Nordeng H (2015) Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers. BMC pregnancy and childbirth 15 (1):321

III: Heitmann K, Svendsen HC, Sporsheim IH, Holst L (accepted 30 October 2015): Nausea in pregnancy – attitudes among pregnant women and general practitioners on treatment and pregnancy care. Scandinavian Journal of Primary Health Care

IV: Heitmann K, Solheimsnes A, Havnen GC, Nordeng H, Holst L (accepted 12 January 2016):Treatment of Nausea and vomiting during pregnancy – a cross-sectional study of 712 Norwegian women. European Journal of Clinical Pharmacology

Reprints were made with permission from the respective publishers.

Contents

1. **Introduction**

In the following introduction, the background to studying NVP, methods and knowledge gaps will be presented. This forms the basis for the PhD thesis.

1.1 Why study treatment of nausea and vomiting during pregnancy (NVP)?

The study of NVP is of interest due to the condition's high prevalence in the pregnant population, its potentially major consequences for both mother and child and its potential for progression to very severe symptoms, leading to hospitalisation. Moreover, NVP has been subject to much debate in recent years, being one of the most frequently given reasons for sick leave during pregnancy (1-3). However, little is known about how women with this condition are treated, also in Norway.

As for the general pregnant population, more knowledge is needed about the safety of use of medicines and herbal remedies against NVP, and their patterns of use. It is necessary to know what is used and by whom. The characterisation of women who use conventional and herbal medicines for NVP is necessary in order to gain a better understanding of the users and/or non-users. In order to improve pharmacotherapy for women with NVP, more knowledge is needed about the rationale for the decision to use conventional and/or herbal medicines or to abstain from use. Although some previous studies have described the treatment of NVP and/or attitudes to treatment, for many countries little research has been done to characterise treatments used for this illness. Furthermore, little is known about various aspects of the treatment of NVP in a Norwegian population. Several cultural and socioeconomic differences characterising women in Norway as compared to other western countries may have an impact on the use of conventional and herbal medicines. The Norwegian population has a high standard of living and is generally highly educated. The healthcare system is well-functioning and provides free and frequent antenatal consultations. In addition,

Norwegian employees are entitled to sickness benefits equivalent to full wages if occupationally disabled due to own illness (4).The sick leave may be fulltime or graded (part-time) (4), e.g. working 50% and being paid sickness benefits equivalent to 50% wages.

Preventing suboptimal and incorrect use of treatment against NVP may lead to substantial improvements in the care of pregnant women suffering from NVP.

1.2 Thalidomide – the tragedy that shaped our beliefs

In the early 1960s, the thalidomide tragedy struck the world, resulting in more than 10,000 children born with major malformations (5, 6). Thalidomide was marketed in 1957 in Germany, and later in over 46 countries worldwide, as a sedative and hypnotic for treating insomnia and anxiety. It was also found to be effective against symptoms of morning sickness (5). In the early 1960s, however, an association between *in utero* exposure to thalidomide and severe congenital malformations was suspected and independently reported by doctors McBride and Lenz (7, 8). As a consequence, the drug was withdrawn from the market (5). The critical period for maternal intake of thalidomide resulting in malformations is found to be between 20 and 36 days post fertilisation, and the risk of congenital malformations after exposure within this period is estimated to be between 20% and 50% (5, 9). Thalidomide intake, as repeated use or even as one single dose, caused a wide range of anomalies, with the most frequently reported being those affecting the extremities, including phocomelia and amelia, and the ears (5, 10). The survival rate is estimated to be between 40% and 70% (5).

The consequences of the above-mentioned tragedy were: 1) the concept of a placental barrier was discarded (9); 2) the promulgation of new drug regulations in the USA stating that the efficacy and safety of a drug must be investigated for the conditions of use prescribed in its labelling (9); 3) the initial exclusion of, and continuing caution about including, women in clinical trials (11). Today, it is clear that most drugs are able

to cross the placenta to some extent (9). Indeed, other drugs are found to be teratogenic, e.g. valproic acid, warfarin and isotretinoin (10). Other agents, such as Bendectin®, were falsely accused of having teratogenic potential, leading to market withdrawal despite the fact that a thorough review by the U.S. Food and Drug Administration (FDA) and regulatory agencies worldwide did not detect any association between the doxylamine-pyridoxine combination and teratogenic effects (12, 13).

A common belief developed as a result of the new awareness; women should preferably abstain from using medicines during pregnancy, especially during first trimester, a belief that is still widespread among the general public, but is also found among healthcare providers and in guidelines. Since the use of conventional medicines is feared during pregnancy, the use of complementary and alternative medicine is embraced by pregnant women due to the common belief that they are safe because of the substances' natural origin (14). However, their efficacy and safety when used during pregnancy is poorly studied, and little is known about the potential for interaction with other supplements and/or conventional medicines. Nevertheless, studies from developed countries have reported that 27% to 93% of pregnant women use medicines, and approximately 40% use herbal medicines (15-18).

Major congenital malformations occur in 1–3% of the general population at birth (10). Among these, it is worth noting that only 2–3% are thought to be related to drug exposure (10). Moreover, the prevalence of congenital malformations has not increased over the last half century despite the introduction of several new pharmaceutical agents on the market (19). Pregnant women get sick, and sick women get pregnant, which means that pharmaceutical treatment is essential for many pregnant women. Because some disease states, if untreated, pose a greater risk to the pregnancy than the treatment itself, e.g. epilepsy, depression and asthma, the avoidance of medical treatment can represent a direct danger to the women and their pregnancies (19). The costs, both psychosocial and financial, of teratogenic therapies are acknowledged. However, what about the costs of inadequately treated diseases of pregnancy – growth restriction,

pregnancy loss, preeclampsia/eclampsia (20), and also severe nausea and vomiting during pregnancy? The situation today is that most medications are marketed without an established safety profile for pregnant women, the result being extensive off-label use during pregnancy (11). Furthermore, there is a lack of development of drugs for use in obstetrics. Consequently, pregnant women are excluded from the therapeutic advances expected from modern drug research and development (11).

1.3 Historical perspectives on the treatment of NVP

The first references to vomiting in early pregnancy date from as early as about 2000 B.C. in a papyrus that is part of the Petrie collection (21). It has since engaged numerous authors who have theorised on the subject. The aetiology has been attributed to various factors during history (21, 22). The first cases of excessive vomiting with fatal consequences reported in the medical literature date back to 1706 by Kerkring, and 1827 by Dance (21, 22). In 1933, Kemp referred to NVP/hyperemesis gravidarum (HG) as a 'disease of theories' (21, 23), a description that is still quite relevant.

Historically, it has been held that vomiting of pregnancy is a psychosomatic illness (24). It has been alleged that women with severe nausea and vomiting transform psychological distress into physical symptoms (24). Several theories have been suggested. For instance, NVP has been described as a reflection of the mother's resentment of the pregnancy, and vomiting as an attempt by the mother to expel the foetus orally (24, 25). Others have proposed that NVP is an unconscious mechanism resulting from a conflictual relationship with one's own mother or husband (24, 25).

Fairweather reviewed treatments against hyperemesis in 1968, restricting the survey to the years after 1938, and concluding that it was clear that no uniform strategy was applied (21). Though some of the treatments are recognised and still applied in today's practice, such as antihistamines, vitamins and chlorpromazine, there are some that are quite obscure (see Figure 1): intramuscular injections of husband's blood, intravenous

honey and inductive current (21). Other approaches cited in the literature include isolating the patient, denying her a vomit bowl and instructing her to vomit in the bed, and leaving it to herself to clean up after vomiting occurs (26). The wide range of types of treatments applied probably reflects the lack of a recognised aetiology.

Note that Fairweather claimed as early as 1968 that '*The value of drug therapy, if any, comes at the stage of morning sickness, when any of the present-day antiemetic group may be used to counter the feeling of nausea. If one can control symptoms at this stage, then it is likely that a large number of women can be prevented from developing excessive vomiting which if prolonged leads to metabolic disturbances'* (21).
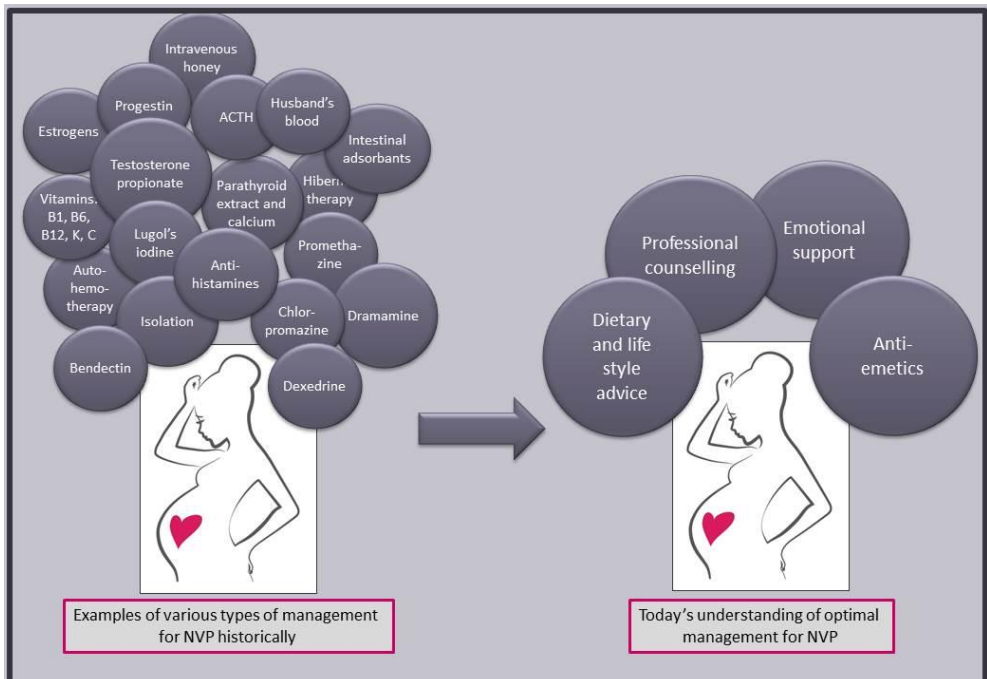
Figure 1. An illustration of the management of NVP, historically and today. Based on Fairweather and selected guidelines (21, 27-36). Abbreviations: NVP, Nausea and vomiting during pregnancy; ACTH, adrenocorticotropic hormone.

1.4 Nausea and vomiting during pregnancy

1.4.1 Prevalence and definition

NVP is one of the most commonly experienced pregnancy complaints, affecting approximately 70% of the pregnant population (37). The symptoms of NVP vary from mild nausea, gradually increasing in severity to frequent and persistent vomiting associated with severe morbidity, therapeutic abortion and even mortality if not treated properly (38-40). Hyperemesis gravidarum (HG) represents the most severe end of the NVP symptom spectrum, affecting approximately 1% of pregnant women (37). HG is considered to be a continuum of NVP following a gradual progression of severity of NVP symptoms (32, 41).

NVP-related diagnoses are clinical diagnoses without uniform criteria (31). In 1968, Fairweather defined HG as vomiting occurring in pregnancy before the 20th week of gestation, and of such severity as to require hospital admission, without coincidental medical conditions (21). It was later revised by others to include persistent nausea and vomiting leading to dehydration, weight loss of more than 5% of maternal pre-pregnancy weight, ketonuria, and electrolyte imbalance (42). The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) uses the codes O21.0 and O21.1 for 'Mild hyperemesis gravidarum' and 'Hyperemesis gravidarum with metabolic disturbance', respectively (43). Mild HG is defined as 'HG, mild or unspecified, starting before the end of the 22nd week of gestation', whereas HG with metabolic disturbance is defined as 'HG starting before the end of the 22nd week of gestation, with metabolic disturbance such as: carbohydrate depletion, dehydration and/or electrolyte imbalance' (43). However, no universally accepted criteria distinguish between the mild and severe disease (31).

The national guidelines issued by the Norwegian Society of Obstetrics and Gynecology (NGF) categorises NVP in three categories: mild, moderate and severe, according to the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE) scale (34, 44). The PUQE

scale was developed by Motherisk, Toronto, Canada and assesses the severity of NVP (44).

NVP is often referred to as a diagnosis of exclusion, and it is important to rule out other possible causes of the symptoms. It is worth noting that NVP that develops after pregnancy week 9-10 is rare, and the presence of fever, abdominal pain and tenderness, diarrhoea, constipation, headaches and palpable goitre is atypical in women with NVP, suggesting another cause than NVP (13, 32, 41, 45) (pregnancy week is in this thesis defined as: gestational week calculated from the last menstrual period before pregnancy). Differential diagnoses include for instance viral and bacterial infections, preeclampsia, food poisoning, gastrointestinal disorders (e.g. gastroenteritis, appendicitis, hepatitis, pancreatitis), pyelonephritis, kidney stones, metabolic disorders (e.g. hyperthyroidism, Addison's disease, porphyria and diabetic ketoacidosis) and diseases of the central nervous system (e.g. migraine headaches and tumours) (13, 27, 32).

1.4.2 Physiology and description of the symptoms

Nausea and vomiting have many causes, of which pregnancy is one (46, 47). The central neural regulation of vomiting is allocated to the vomiting centre and the chemoreceptor trigger zone (CTZ) in the *area postrema* located in the medulla (46, 47). The CTZ is not protected by the blood-brain barrier and is therefore sensitive to chemical stimuli, also by circulating toxins. CTZ is an important source of stimulation of the vomiting centre and the main site of action of many antiemetic drugs (46, 47). The CTZ has many dopamine D_2 receptors and serotonin $5HT_3$ receptors, and the transmission from the vestibular apparatus to the vomiting centre involves cholinergic and histaminergic synapses (46, 47). The vomiting centre receives afferents from the limbic cortex, CTZ, *nucleus solitarius*, spinal cord and the vestibular system. Though not fully known, the neurotransmitters considered to be involved in the control of vomiting are acetylcholine, histamine, serotonin and dopamine.

Even though NVP is known colloquially as morning sickness, NVP symptoms occur after midday in the majority of the women with NVP (41). Typically, the symptoms initiate in the 6th gestational week, 90% experience the onset of NVP before the end of week 8, with a peak in intensity around weeks 8–13, before gradually declining during the second trimester (48-50). For most women, the symptoms resolve by the end of week 16. However, 10% still experience symptoms after pregnancy week 20-22 (48, 49, 51). NVP typically follows an episodic pattern, in which 85% of the women with NVP experience at least two episodes with symptoms per day, the majority of which (70%) last 1–4 hours (41). Nausea is repeatedly described as the most distressing symptom (41, 52-54). Vomiting occurs in approximately half of the pregnant population (48, 49, 51). Vellacott et al. reported daily vomiting in 28% of the women with NVP (50). One study revealed that the intensity of NVP at 11 weeks of gestation was comparable to the intensity of nausea symptoms experienced by patients with moderately emetogenic chemotherapy (49). Note that HG patients were excluded from this study. Although the prevalence of NVP gradually declines in the second trimester, for the women who continue to experience NVP, the intensity of symptoms tends to remain fairly stable (49).

A variety of instruments have been utilised to measure the severity of NVP symptoms, including the Rhodes Index, the Nausea and vomiting in pregnancy instrument, the McGill Nausea Questionnaire, the Hyperemesis Impact of Symptoms Questionnaire, and PUQE (44, 49, 55-58). The severity of symptoms has also been determined based on the presence of nausea with/without vomiting, the numbers of hours of nausea, the number of vomiting episodes, diagnosis of HG, presence of HG defined as admission to hospital with/without dehydration, electrolyte disturbances, 5% pre-pregnancy weight loss, ketonuria or single/multiple admissions (41, 48, 59-62). This heterogeneity makes comparison of symptom severity between different studies challenging.

1.5 Aetiology

Comprehending the full aetiology of an illness may lead to the identification of effective treatments. Several mechanisms have been proposed in an attempt to explain the aetiology of NVP, but no firm conclusions can be drawn, due to the varying definitions of HG and/or NVP, small studies and differing assay methodology applied in the hormone measurement studies (63). It is possible that HG is caused by a yet unidentified factor, or that HG is the end result of various conditions. However, NVP/HG is frequently assumed to have a multifactorial cause (40). While NVP affects the large majority of pregnant women to some extent, only a minority develop severe NVP/HG. In order to explain why some women develop more severe symptoms, Bogen and Goodwin both introduce the concept of differences in the individual's response to the causative agent, depending on her susceptibility mediated by vestibular, gastrointestinal, olfactory and behavioural pathways (64, 65). The fact that no single theory has been identified certainly complicates the management of this condition (63).

Several factors have been associated with NVP in the literature (41). The results from many of the studies are conflicting, however, probably due to differences in methodologies and definitions of NVP and HG. Again it is difficult to distinguish between risk factors for NVP and HG, as the definitions for the two conditions vary in the literature. However, in an extensive review by Gadsby and Barnie-Adshead, the following factors were identified as being associated with an increased likelihood of NVP or HG: NVP in previous pregnancies, non-smoking, nausea when previously taking an oral contraceptive, hydatidiform mole, twin pregnancy, increase in food cravings and aversion, and excessive caffeine-intake (41). HG alone was associated with having a mother who had suffered from HG, younger age (<26 years of age), nulliparity, a previous unsuccessful pregnancy, reduced maternal weight gain in current pregnancy and female offspring (41).

Various theories have been proposed for the aetiology of NVP, but a combination of several factors is probably involved (66):

- **Evolutionary perspective**: One theory is that normal levels of NVP protect pregnant women and their foetuses against harmful substances in food (67).

- **Genetic**: NVP and HG show patterns of familial aggregation. A higher risk of severe NVP/HG is found among women with mothers and/or sisters who have experienced severe NVP/HG (50, 68, 69). Monozygotic female twin pairs are found to be more concordant than dizygotic female twin pairs in relation to experiencing NVP (70).

- **Endocrine**: Hormonal changes occurring in pregnancy are thought to be part of the aetiology of NVP and HG, and the most commonly proposed hormones involved include the human Chorionic Gonadotropin (hCG), oestrogen, progesterone and thyroid hormones (71). Eleven of 15 studies published since 1990 showed a significantly higher level of serum hCG among women with HG compared to controls, but its role in the pathogenesis remains elusive (63). Furthermore, the current literature does not suggest that the aetiology of HG can be explained by the role of progesterone or oestrogen alone, and their relationships with NVP have been inconsistent between studies (63, 72). Since hCG and thyroid stimulating hormones are structurally related, the observed association with hyperthyroidism may be explained by characteristics facilitating highly stimulating properties of the thyroid gland among women with HG (63, 65, 73). However, since hyperthyroidism itself is seldom a cause of nausea and vomiting, the focus is switched back to hCG (65).

- **Gastric dysrhythmias**: Changes in gastric rhythmic activity may contribute to NVP (74). The intensity of nausea is significantly greater in pregnant women with gastric dysrhythmias than in those with normal electrogastrographic patterns (74).

- *Helicobacter pylori* (*H. Pylori*)**:** There is evidence suggesting an association between *H. pylori* infection and hyperemesis gravidarum (75, 76). Whether treatment for *H. pylori* in *H. pylori*-positive HG women is a useful strategy for shortening symptoms

of HG has not been thoroughly studied, but this may represent a new therapeutic option (76).

- **Psychological factors**: As already described in section 1.3, NVP has been believed to have a psychosomatic explanation. However, both Buckwalter and Munch question the validity of these beliefs due to the lack of methodologically sound studies (24, 77). Both authors draw attention to the problem of gender bias to explain the pervasiveness of the assumption that HG is of psychosomatic origin. It is suggested that there is a psychological component to more severe NVP and HG that can be explained by the severe, continuing and incapacitating physical symptoms that *result* in psychological stress and trauma (78). Indeed, symptoms of depression and anxiety have been associated with NVP and HG, as well as posttraumatic stress syndrome (79-82).

In conclusion, the inconclusive evidence means that a single cause cannot be determined (63). Though some of the proposed mechanisms provide reasonable explanations, there is still a need for more knowledge and understanding of the causes and their possible interconnection (63, 65). Moreover, studies on NVP should include information about these factors if possible, as they may be important to our understanding of this illness. As long as NVP's exact aetiology is unknown, treatment is problematic since the optimal targets are unidentified.

1.6 Impact of NVP

The importance of studying NVP becomes apparent in light of current knowledge of the possible impact of NVP on women, their families and on society.

1.6.1 Pregnancy outcomes and foetal complications

NVP symptoms in general have been associated with decreased risk for miscarriage and early delivery (41, 72, 83). However, there is evidence that severe HG is associated with a higher incidence of children with low birth weight (LBW), small for gestational age

(SGA) children and preterm delivery (84). However two large registry-based studies, recently conducted in Norway, detected no clinically significant impact on HG on pregnancy outcomes (85, 86). Some authors argue that HG itself is not thought to be a risk factor for the negative pregnancy outcomes, which are instead thought to be mediated through low weight gain during pregnancy (<7 kg) as a consequence of severe NVP/HG (87, 88). Women with weight gain of <7 kg has been found to have an increased risk of having SGA-children and preterm delivery (87, 88). Little is known about the long-term health effects on infants born to mothers whose pregnancies were complicated by HG. Of potential relevance to HG is the findings by Roseboom et al., who found that poor maternal nutrition during pregnancy, especially in early gestation, during the Dutch famine, was shown to imply lasting negative consequences for the child's health, independently of the child's size at birth (89). Indeed, two studies found, firstly, that children aged 8 to 9 years had a higher risk of neurodevelopmental diagnosis, and, secondly, that adults exposed to HG *in utero* had a higher risk of behavioural or emotional disorders (90, 91). A third study reported lower insulin sensitivity among children aged 4 to 11 years born to mothers who had experienced HG, compared to controls (92). It has also been speculated whether HG offspring have an increased risk of cancer, but no firm evidence yet exists (93).

1.6.2 Maternal complications

Psychosocial morbidity in pregnant women with NVP is substantial, and in many cases, underemphasised (72). Awareness of the high burden that NVP represents for the women highlights the need to take this condition seriously.

NVP has been shown to have a profound impact on a woman's life, negatively affecting quality of life, daily activities, her relationship with her partner, parenting, social functioning and occupation (52, 53, 57, 94, 95). Women with moderate to severe NVP have been found to have a quality of life comparable to women with recent breast cancer, myocardial infarction or postpartum depression (94). Moreover, women with

NVP had lower Short Form-36 domain scores in physical functioning, physical role, bodily pain, vitality, social functioning and emotional role compared to healthy pregnant women and women with clinical depression (57). Though the effects are magnified when symptoms are moderate or severe, even mild NVP can have significant adverse effects on a woman's life (53, 95).

Women describe feelings of isolation, fatigue, depression and helplessness due to nausea (53, 82, 96). Family planning is affected in women with severe symptoms; up to 15% of those with severe symptoms have been reported to terminate an otherwise welcome pregnancy, and almost 40% are reported to being considering or planning to avoid further pregnancies, illustrating how debilitating severe NVP can be (38, 39, 96, 97). Importantly, the women who performed elective termination of pregnancy were more than three times more likely to report a negative attitude from their caregiver than women who did not terminate their pregnancy (38).

Although Lacasse et al. found an inverse association between increased severity of NVP and decreased quality of life (94), work by Munch et al. suggests that *perceived* physical symptom severity and multiple psychosocial factors are equally or more important contributors to low quality of life than having an HG diagnosis (98). Women with NVP may experience an equally significant negative impact on quality of life as HG patients if they perceive their physical symptoms to be severe (98). This is in line with Mazzotta et al., who concluded that psychosocial morbidity is evident across the different degrees of NVP, even among women with mild NVP symptoms (53). Note that among women with mild symptoms, 21%, 36% and 43% reported feeling depressed due to NVP always or most of the time, an adverse effect on their relationship with a partner and an adverse effect on the partner's daily life, respectively (53). Furthermore, compared to vomiting, nausea alone is reported three times more frequently to be the most troublesome symptom (53).

If inadequately managed, HG can cause significant maternal complications as a result of vitamin deficiency, electrolyte abnormalities, dehydration, protein and energy malnutrition, as well as psychological morbidity (40, 99). Vitamin B1 (thiamine) deficiency can cause Wernicke's encephalopathy (40, 100, 101). Acute encephalopathy is triggered by the ingestion of carbohydrate-rich food and intravenous administration of dextrose or glucose, since the metabolism of the carbohydrates consumes the available thiamine (40, 100). Vitamin B6 (pyridoxine) and vitamin B12 (cobalamin) deficiencies can result in anaemia and peripheral neuropathies (40, 102). An abnormal coagulation profile and bleeding have also been described as a result of Vitamin K deficiency (103), while hypokalaemia and hyponatraemia can cause central pontine myelinosis (101). Increased risk of thrombosis is due to dehydration and immobility (40). In addition, Mallory Weiss tears (oesophageal rupture) have been described as a consequence of mechanical forces (40, 63).

Fatal outcomes due to HG are rare nowadays, which can be attributed to better treatment with restoration of fluid and electrolyte balance, which was more thoroughly understood in the early 1940s (21, 99, 104). A dramatic decrease in the maternal mortality rate was observed in the UK as a result, dropping from 159 per million in the period 1931to1940, to 3 per million observed in the period from 1951 to 1960 (104). However, the latest death in Norway as a consequence of HG was in 2004, as a result of malnutrition (105, 106).

1.6.3 Socioeconomic consequences

NVP is one of the most common reasons for sick leave during pregnancy (3), and it represents a significant socioeconomic burden for women and for society (107, 108). HG is also responsible for large expenditures, being the most common reason for hospitalisation in the first half of pregnancy and the second most common reason for hospitalisation during pregnancy overall (109, 110). Moreover, about 25% of women

with HG require multiple admissions (41). SGA and LBW-children are also at risk of needing costly neonatal and paediatric treatment.

1.7 Management of NVP

Due to the multi-faceted aetiology of NVP so far described, it is not surprising that treatment has been attempted by countless methods and drugs throughout history (21) (see also Figure 1). However, as no exact aetiology has been determined, today's treatments aim to treat the symptoms, not the illness. The goal of treatment should be to improve the symptoms while at the same time minimising maternal and foetal complications and risks (31). As elaborated above, severe NVP symptoms have been associated with severe morbidity and shown to have major impact on the women's lives (72), implying that preventing, or reducing the intensity of severe symptoms should be of high priority.

A multimodal, individually tailored approach is usually needed to achieve this goal. The choice of treatment should be based on the severity of symptoms and their impact on the woman. Treatment ranges from dietary modifications, pharmacological treatment to total parenteral nutrition (72).

Treatment of early symptoms may prevent progression to HG and more serious complications and hospitalisation (32). The benefit of early treatment was discussed already in 1968 by Fairweather, who argued that, if the symptoms can be controlled at 'the stage of morning sickness' it is likely that the development of excessive vomiting will be prevented in many cases (21), which is a viewpoint consistently held in North American guidelines (30, 32). The findings of Neutel and Johansen support this (12, 111). Bendectin®, a combination of doxylamine succinate and vitamin B_6/pyridoxine (also including dicyclomine before 1976), was the drug of choice for NVP in the USA and several other countries under other trade names from 1956 to 1983 (112). After the withdrawal of the antiemetic Bendectin® from the market in 1983, there was a marked

increase in the hospitalisation rates due to severe NVP/HG between 1983 and 1989 following reduced sales of Bendectin® (see Figure 2) (12, 111). The Canadian generic product Diclectin®, a combination of doxylamine and vitamin B6, remained on the Canadian market, and in 1990, its use started to increase. In the period 1992–1995 a reduction in the number of hospitalisations due to severe NVP/HG was observed (111).
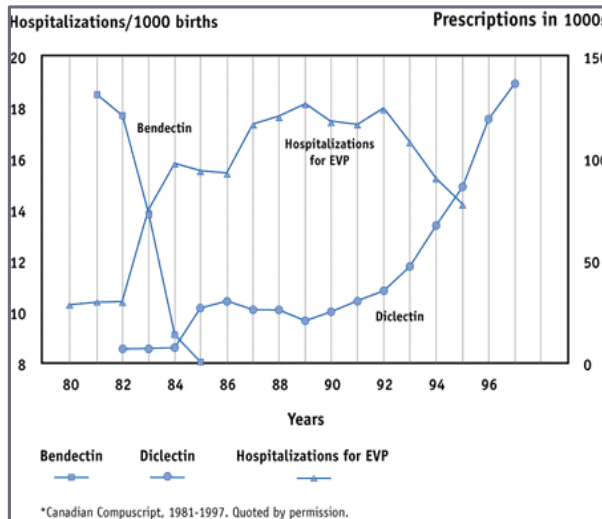
Figure 2. From: Neutel CI: **Variation in rates of hospitalisation for excessive vomiting in pregnancy by Bendectin®/Diclectin® use in Canada**. In: Nausea and Vomiting of Pregnancy : State of the Art 2000. edn. Edited by Koren G. Toronto, Canada: Motherisk; 2000. Reprinted with permission from Koren, G.

Though no rigorous studies are available to verify this, pre-emptive treatment of NVP among women with a history of severe NVP or HG was found to reduce the risk of moderate and severe NVP symptoms (113, 114). Furthermore, prophylactic treatment of nausea and vomiting is a common strategy applied to prevent nausea and vomiting related to other conditions, such as chemotherapy and motion sickness (115, 116). Together, these strategies indicate that it is advantageous to start treatment before symptoms have become more severe.

According to a Canadian study, only half of the women with NVP had been asked about the severity and intensity of their symptoms, and even fewer (22%) were asked about their symptoms' impact on daily tasks (117), illustrating that there is a need for improvements in pregnancy care for women with NVP.

Various guidelines addressing the treatment of NVP/HG exist in Norway and internationally (27-36). For the purpose of this thesis, the following guidelines have been reviewed, with specific focus on the drugs available in Norway and/or recommended in Norwegian guidelines: Norwegian guidelines, such as the National clinical guideline for antenatal care, Norwegian Medicines Handbook, Norwegian Electronic Medical Handbook (NEL), and the Obstetric Guidelines issued by the Norwegian Society of Obstetrics and Gynecology (NGF) (33-36); and other major guidelines considered relevant, such as UpToDate, National Institute for Health and Care Excellence (NICE) guidelines, BMJ Best Practice, and the North American guidelines issued by the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada and the Motherisk (27-33). The Norwegian guidelines, together with NICE guidelines, are generally more restrictive than the other international guidelines in that they specifically state that NVP is considered a normal part of being pregnant, that pharmacologial treatment is rarely necessary and that one should be generally restrictive as regards the use of antiemetics (28, 34-36).

1.7.1 Dietary and lifestyle changes

The guidelines typically include recommendations to start with advice about food and dietary changes, avoidance of triggers and treatment with alternative approaches such as acupressure and ginger (27-36). Dietary and lifestyle changes usually include advice about eating small and frequent meals, avoiding spicy or fatty foods, and eating bland or dry foods and foods that are higher in protein. There is little scientific evidence of the effect of dietary changes on nausea, although some evidence supports the view that protein-predominant meals reduce nausea (118). In addition, a Norwegian study found that women adhering to a diet characterised by fish, vegetables and whole grain prior to pregnancy were less susceptible to developing HG (119). Adequate intake of liquid is important to avoid dehydration, and cold beverages, carbonated or sour, in small amounts between meals are thought to be better tolerated by women (45). Several guidelines refer to the work by Bischoff that describes dietetic strategies of relevance to

the management of nausea (120). In addition, avoidance of triggers such as odours, heat, humidity, noise, and visual and physical motion is recommended. Other recommendations include having a snack in bed before getting up in the morning, and getting enough rest. Motherisk in Toronto, Canada has extensive clinical experience and has issued detailed dietary and lifestyle advice, see Box 1.

Box 1. *Dietary and life style advice adapted from Maltepe and Motherisk (45, 121).*

Dietary strategies
- Eat small amounts of food every 1 to 2 hours. Avoid feeling too hungry or thirsty.
- High-carbohydrate, low-fat foods are easier to digest.
- Eat bland, dry or salty foods. Avoid spicy, fried and/or high fat foods.
- Add any source of protein to each meal and snack (such as nuts, seed, dairy etc.).
- Do not eat and drink at the same time, try to drink 20 to 30 minutes before or after meals and snacks
- Aim at 8 cups of daily fluid intake. Drink colder fluids, such as ice chips, slushies, popsickles or smoothies to increase tolerability.
- Consider adding oral rehydration products such as coconut water, sport drinks or jello made with unflavoured electrolyte solution.
- Consider adding liquid supplements, bars or puddings if unable to keep food down.
- For constipation, try to increase dietary fibre intake along with fluid.

Life style strategies
- Get plenty of sleep and rest.
- To minimize food and odour aversions, ventilate, get fresh air, consume meals lukewarm/cold.
- To reduce metallic, bitter, sour or odd taste in mouth, try candies or gums, and drink ice-cold fluids
- Have a snack before getting up in the morning.
- Spit out excess saliva, and do frequent mouthwash.
- Iron in the prenatal multivitamin may case additional NVP and/or constipation. If normal iron level, try to switch to a multivitamin with lower iron and add folic acid. If low iron levels, split prenatal vitamin taking one half in the morning and one half in the evening.
- Treat symptoms of heartburn and reflux which may aggravate NVP symptoms.

Bottom line
- **Eat anything that agrees with you and stays down.**

1.7.2 Complementary and alternative medicine (CAM)

Ginger

Ginger is included in all the reviewed guidelines. Ginger rhizome (*Zingiber officinale* Roscoe) has a long tradition for use against nausea (122), and is one of the most commonly used herbs during pregnancy (14). Several of the studies published in the last decade report prevalence rates of over 10% (17, 123-125). The mechanism of action remains uncertain, although it is proposed that it is attributable to the ability of the components of ginger to affect serotonin and muscarinic receptors in the gastrointestinal tract (126). A possible antiemetic effect via the central nervous system has also been proposed (127).

The effectiveness of ginger against NVP has been investigated in several studies (Table 1), and it has been found to be more effective than placebo, equally or more effective than vitamin B6, and as effective as acupressure, pyridoxine-doxylamine and dimenhydrinate (128-140). Moreover, when compared to metoclopramide, there were no statistically significant differences in the observed trend of nausea or vomiting severity (141). However, the authors conclude that metoclopramide is more effective than ginger, but this is difficult to read from the published results (141). The most commonly used doses were between 1 g and 1.5 g per day of dried ginger root powder equivalent. One review investigating the effect of ginger on relieving NVP reports that ginger is superior to placebo (142). This is supported by a second review concluding that ginger relieved nausea symptoms, but did not significantly affect the number of vomiting episodes (143). The latest Cochrane review of treatments of NVP concludes that ginger *may* be helpful to women, but that there is limited and inconsistent evidence of its effectiveness (144). The conflicting conclusion is probably due to the stricter study inclusion criteria applied by the authors of the Cochrane review.

Information about the safety of ginger use during pregnancy is mainly derived from the clinical trials, which were generally underpowered to detect any differences between the

groups (144). Nevertheless, no increased risk of negative pregnancy outcomes is reported (143). Most textbooks therefore classify ginger as safe during pregnancy, which is mainly based on a lack of case reports of negative outcomes (9, 145, 146). Caution is therefore recommended (9, 145, 146). Some specific concerns are also raised by certain authors. Women with a history of miscarriage, vaginal bleeding, or clotting disorder are advised to avoid ginger during pregnancy (147), and it is deemed to be contraindicated close to labour due to a feared increased risk of post-partum haemorrhage (148). These concerns probably stem from ginger's ability to inhibit thromboxane synthetase and thereby platelet aggregation *in vitro* (149). However, the consequence of this property *in vivo* is controversial (150-152). Backon has also raised a theoretical concern about ginger's ability to affect testosterone receptor binding which may have implications for the sex differentiation of the foetal brain (153), but this has not been confirmed by other studies. One study has been conducted to specifically investigate the safety of use of ginger during pregnancy (154). The study, which included 187 women, did not detect any statistically significant differences between the ginger group and the control group with respect to malformations, live births, spontaneous or therapeutic abortions, still birth, birth weight or gestational age after ginger use during pregnancy (154).

Commonly reported side effects include heartburn and belching, and higher doses of ginger seem to correlate with more heartburn (132, 143). Many women suffering from NVP also struggle with heartburn and reflux problems (155) that, consequently, may be exacerbated by ginger intake. Though ginger has proven effective against NVP in many studies, a recent survey among women with HG in the UK reported unpleasant side effects such as pain and/or burning during vomiting and acid reflux or heartburn, as well as lack of effectiveness, thereby implying that ginger should not be recommended to the HG patient group (156).

In line with several of the guidelines, the Norwegian guidelines from NGF recommend a maximum ginger dose of 1000 mg per day (34).

Table 1. Overview of randomised controlled trials evaluating the effectiveness of ginger for nausea and vomiting in pregnancy.

Study	Design	n	Period of gestation	Duration of treatment	Ginger dosage (preparation) and control substance	Main outcome	Adverse reactions	Adverse reactions regarding pregnancy outcome
Fischer-Rasmussen et al. 1990 (133)	Double-blind RCT, cross-over	30	<20 w	4 d	250 mg x 4 (capsules) Placebo capsules x 4	Ginger was better than placebo at diminishing or eliminating hyperemesis symptoms	No side effects were observed	No adverse effects were detected
Vutyuavanich et al. 2001 (128)	Double-blind RCT	70	≤17 w	4d	250 mg x 4 (capsules) Placebo capsules	Ginger is more effective than placebo in relieving the severity of nausea and vomiting	Headache, abdominal discomfort, heartburn, diarrhoea.	No adverse effects were detected
Keating and Chez 2002 (129)	Double-blind RCT	26	First trimester	2 w	250 mg x 4 (syrup in water) Placebo syrup x 4	Ginger was more effective than placebo in reducing nausea and stopping vomiting	Not reported	No adverse effects were detected
Sripramote and Lekhyananda 2003 (130)	Double-blind RCT	138	≤16 w	3 d	500 mg x 3 (capsules) 10 mg vitamin B6 x 3 (capsules)	Both ginger and vitamin B6 significantly reduced the degree of nausea and the number of vomiting episodes, with no significant difference between the two	Drowsiness, heartburn	Not reported
Willetts et al. 2003 (132)	Double-blind RCT	120	<20 w	4 d	125 mg extract, equiv. to 1.5 g dried ginger, x4 (capsules) Placebo capsules x 4	Ginger was more effective than placebo in reducing the nausea and retching, but equally effective regarding vomiting	Reflux and heartburn	No adverse effects were detected

Study	Design	N	Gestation	Duration	Intervention	Results	Adverse effects	Safety
Smith et al. 2004 (131)	Randomised controlled equivalence trial, single blinded	291	8 - 16 w	3 w	350 mg x 3 (capsules) 25 mg vitamin B6 x 3 (capsules)	Ginger was therapeutically equivalent to vitamin B6 in alleviating nausea, dry retching, and vomiting.	Burning sensation, belching	No adverse effects were detected
Chittumma et al. 2007 (136)	Double-blind RCT	123	≤16 w	4 d	2 capsules of 325 mg ginger x 3 2 capsules of 12.5 mg B6 x 3	Ginger was more effective than vitamin B6	Heartburn, sedation and arrhythmia, mild, needed no treatment	Not reported
Pongrojpaw et al. 2007 (135)	Double-blind RCT	170	<16 w	7 d	500 mg x 2 (capsules) 50 mg dimenhydrinate x 2	Ginger is as effective as dimenhydrinate in the treatment of nausea and vomiting	Fewer side effects than dimen-hydrinate, heartburn and drowsiness	Not reported
Ensiyeh and Sakineh 2008 (134)	Double-blind RCT	70	≤17 w	4 d	500 mg x 2 (capsules) 20 mg vitamin B6 x 2 (capsules)	Ginger is more effective than vitamin B6 in relieving the severity of nausea, and is equally effective for decreasing the number of vomiting episodes	Not reported	No adverse effects were detected
Basirat et al. 2009 (157)	Double- blind RCT	62	7 - 17 w	4 d	Ginger biscuits containing 500 mg ginger as fine powder x 5 Placebo biscuits x 5	Ginger was significantly more effective than placebo in reliving symptoms of nausea	Heartburn and dizziness	No adverse effects were detected

Study	Design	N	Gestation	Duration	Intervention	Findings	Side-effects	Adverse effects
Ozgoli et al. 2009 (137)	Single-blind RCT	67	<20 w	4 d	250 mg x 4 (capsules) / Placebo capsules x 4	Ginger was more effective than placebo in relieving nausea and vomiting	No side-effects reported	Not reported
Biswas et al. 2011 (140)	Single-blind RCT	63	6-16 w	21 d	150 mg x 3 (tablets) / Doxinate (10 mg doxylamine and 10 mg pyridoxine) x 2-3	No difference between the groups with respect to episodes of nausea or vomiting	No severe or serious adverse events detected	No adverse effects detected
Mohammad-beigi et al. 2011 (141)	Double-blind RCT	102	<20 w	5 d	200 mg of ginger essence x 3 (capsules) / 10 mg metoclopramide x 3 (capsules / Placebo capsules	Ginger and metoclopramide were statistically more effective in reducing NVP symptoms compared to placebo, but not statistically different when compared to each other	Not reported	Not reported
Saberi et al. 2013 (138)	RCT	159	<16 w	4 d	250 mg x 3 (capsules) / Acupressure (Sea band)	Ginger was more effective than acupressure in relieving mild to moderate NVP	Not reported	Not reported
Saberi et al. 2014 (139)	RCT	120	<16 w	4 d	250 mg x 3 (capsules) / Placebo capsules	Ginger is more effective than placebo in reducing NVP in women with mild to moderate nausea	Not reported	Not reported

Abbreviations: RCT, randomised controlled trials; w, weeks of gestation; d, days; NVP, nausea and vomiting during pregnancy

Acupuncture and acupressure

Acupressure and/or acupuncture of the P6 (Neiguan point) are mentioned in several of the guidelines (27-36). Though the therapies appear to be safe to use during pregnancy (30, 31), it is pointed out that the evidence supporting their use is scarce, with conflicting results and the existence of significant methodological flaws (32, 144, 158). The Cochrane review from 2014 concludes that there is some evidence of the effectiveness of P6 (Neiguan) and auricular acupressure in use against NVP (144), which is in line with another review (158). However, the authors found no significant benefit of acupuncture (P6 or traditional) for NVP (144).

Vitamin B6

Vitamin B6, pyridoxine, is recommended either as a single agent or in combination with doxylamine or another antihistamine (27, 29-34). Vitamin B6 is found to be beneficial for use against NVP (159, 160). According to Matthews et al., who were behind the Cochrane review, vitamin B6 is found to be effective in reducing nausea, but to have no effect on vomiting (144), and a daily dose of 10 mg was favoured over a lower dose of 1.28 mg (161). The Norwegian guidelines from NGF recommend a treatment regime of either 25 mg 4 times daily or 40 mg 2 times daily, not exceeding 200 mg daily (34). Tablets containing 40 mg are available in Norway.

It is worth noting that the Norwegian Medicines Handbook states that vitamin B6 has no more effect than placebo on NVP (35). Moreover, NICE does not currently recommend pyridoxine due to concerns about toxicity at high doses (28). Cases of neuropathy have been described after high doses of pyridoxine intake, substantially exceeding the doses recommended for NVP (102). In most cases the intake was higher than 2 g, although an intake of 200 mg over a long period of time (>3 years) was also reported (102). However, as one of the constituents of Diclegis[®]/Diclectin[®], and formerly Bendectin[®], pyridoxine's safety has been widely studied, and no increased risk of birth defects has been detected (162).

1.7.3 Pharmacological treatment

There are several antiemetics available to help alleviate NVP symptoms. The medicines described in the Norwegian guidelines and/or available on the Norwegian market are listed in Table 2.

Table 2. *An overview of medicines for the treatment of NVP available on the Norwegian market or described in the Norwegian guidelines.*

Generic name	Product name on Norwegian market
Meclizine	Postafen®
Cyclizine	Marzine®
Promethazine	Phenergan®
Metoclopramide	Afipran ®
Prochlorperazine	Stemetil ®
Chlorpromazine	Largactil® (currently not marketed)
Ondansetron	Zofran ®

The best course of treatment on the basis of evidence-based individual evaluations of effect and safety should be sought. UpToDate recommend that patients are continued on a particular medicine for several days to determine whether the symptoms are improving (31). While Canadian guidelines and UpToDate advise adding new medicines in their algorithm (29-31), the Norwegian guidelines from the NGF state that a medicine is traditionally discontinued before starting up a new one, adding that, in theory, a combination of medicines acting through different mechanisms of action may be beneficial, but that the evidence of a potential benefit is scarce (34). However, combination therapy is a commonly applied strategy in the treatment of chemotherapy-induced nausea and vomiting (115). According to the Motherisk NVP protocol, women should be advised to take their medicines daily and consistently to control the symptoms, and gradually taper off the medicines upon improvement (45). UpToDate recommends continuing the drug regimen that is effective until the patient has been asymptomatic for at least a week before discontinuing the medicines (31).

Antihistamines

Antihistamines are regarded as first line treatment when dietary and lifestyle changes and/or complementary therapies fail to relieve the symptoms (28, 30-36). Antihistamines act directly on the vomiting centre and also on the vestibular system (47). Cholinergic and histaminergic synapses are involved in the transmission from the vestibular system to the vomiting centre (47). The antihistamines recommended in the Norwegian guidelines are meclizine and promethazine (33-35), while cyclizine is included in the Danish guidelines and UpToDate (31, 163).

Antihistamines are reputed to be safe to use during pregnancy. A meta-analysis of 24 trials involving more than 200,000 women found no increased risk of teratogenic effects after use of antihistamines during the first trimester (164). A re-analysis of the data included in the study by Seto et al. identified a total study population of 139,414 women of whom 23,485 had exposure to antihistamines, and no increased risk of malformations was detected (165). Together with a meta-analysis by Mazzotta and Magee, a Swedish study based on the Medical Birth Registry reinforced the perceived safety of antihistamines (166, 167). The Swedish study, which includes data on meclizine, cyclizine and promethazine, actually found a lower risk of low birth weight, prematurity, being small for gestational age and malformations associated with use of antihistamines (166). This is supported by data from the meta-analysis, which detected no increased risk of congenital malformations (166, 167). While meclizine was associated with increased risk of cleft palate in one study, this finding was only based on five exposed cases (168), and several other studies have not replicated this finding (169). A Swedish study including >16,000 exposed cases detected no increased risk of malformations, preterm birth, low birth weight, short body length and small head circumference after use of meclizine during pregnancy (170). Hence, a recent review focusing on antihistamines and birth defects concluded that the literature on safety of antihistamine use during pregnancy is generally reassuring, particularly for the first-generation H_1-receptor antagonists (169).

While the latest Cochrane review concluded that there was limited evidence to support the use of pharmacological agents to relieve mild to moderate nausea, the meta-analysis by Mazzotta and Magee indicates that antihistamines are effective against NVP (144, 167).

The delayed release product containing doxylamine, 10 mg, in combination with pyridoxine, 10 mg, is probably the most extensively studied agent among the antihistamines (112). It has been studied for both effectiveness and safety (112). This combination in a delayed release formulation has been available since 1979 in Canada, and it was recently also approved by the FDA (112). According to current evidence, this combination is safe for mother and foetus, and superior to placebo for relieving NVP symptoms (162, 171, 172). The standard dosage regimen of the doxylamine-pyridoxine combination is up to four tablets per day (one in the morning, one in the afternoon and two at bedtime) (45).

Promethazine is primarily an H_1-receptor antagonist classified under antihistamines according to the Anatomical Therapeutic Chemical (ATC) classification system (173), although it is also a weak dopamine antagonist (31). Promethazine was found to have similar therapeutic effects to metoclopramide in patients hospitalised for HG (174), but the latter had a better side effects profile.

The Norwegian guidelines recommend meclizine 25 mg 1-2 times daily or promethazine 25 mg 2-3 times daily (33, 34). Cyclizine is also available on the Norwegian market, but is not included in the Norwegian guidelines. Danish guidelines recommend cyclizine 50 mg three times daily (163).

Common side effects of antihistamines are drowsiness and sedation (46).

Dopamine antagonists

If antihistamines do not provide sufficient relief, a dopamine antagonist is usually the next step (27, 29, 31, 33-35). The dopamine antagonists mentioned in the Norwegian guidelines are metoclopramide, prochlorperazine and chlorpromazine (33-35).

Metoclopramide is a D_2 receptor antagonist that exerts its action in the chemoreceptor trigger zone and through a peripheral prokinetic action that increases the motility of the oesophagus, stomach and intestine (46). Metoclopramide may therefore be helpful for women with indigestion, or who vomit indigested food eaten many hours earlier (45).

Large cohort studies have failed to demonstrate an increased risk of major malformations, low birth weight, preterm delivery, perinatal death, spontaneous abortion or stillbirth after exposure to metoclopramide during pregnancy (175, 176).

Two randomised controlled trials (RCTs) found metoclopramide to be as effective as promethazine and ondansetron (174, 177), while another RCT found ondansetron to be superior to metoclopramide in controlling severe vomiting (178). A study that evaluated the effectiveness of three pharmaceutical regimens found that the regimen combining pyridoxine and metoclopramide was superior to either monotherapy of prochlorperazine or promethazine in the management of NVP (179). A retrospective database analysis, which compared outpatient regimes of subcutaneous infusion of ondansetron or metoclopramide for HG, found that more patients altered their treatment regime from metoclopramide to ondansetron than vice versa, with the most common indications being persistent severe symptoms or side effects (unspecified) (180). Lombardi et al. found that subcutaneous metoclopramide improved symptoms of NVP in 89% of the women, and alteration of therapy to subcutaneous ondansetron was required by 10.7% of the women, who were more likely to have a PUQE score ≥13 (181). As argued by Klauser et al., although each patient may respond differently to treatment due to the unique character of NVP, these results may indicate that ondansetron is superior to metoclopramide in managing severe NVP symptoms (180).

The Norwegian guidelines recommend 10–20 mg of metoclopramide three times daily as a tablet or a suppository (34). However, the suppositories were recently withdrawn from the Norwegian market.

The phenothiazines prochlorperazine and chlorpromazine are antipsychotics that are also used as antiemetics during pregnancy (46). They are primarily D_2 antagonists, but they also have some blocking effects on histamine and muscarinic receptors (46). Though there are isolated case reports of children born with malformations after exposure to prochlorperazine during pregnancy, Briggs et al. conclude that most evidence generally points to prochlorperazine being safe during pregnancy when used occasionally and in low doses (182-185). These findings were supported by two other studies that failed to detect increased risk above baseline risk for birth defects among 704 and 224 infants, respectively, who were exposed to prochlorperazine during the first trimester (185, 186). Little evidence of effectiveness exists, although prochlorperazine seems to be effective for some patients (179). Norwegian guidelines recommend 5-10 mg tablets of prochlorperazine two to three times daily, or 25 mg in one daily administration as a suppository (33, 34).

UpToDate specifically states that chlorpromazine is reserved for refractory cases (31). Some concerns have been raised about the high doses used in the treatment of psychiatric illnesses, although the doses used in the treatment of NVP are much lower (184). Consequently, though literature documenting the safety and effectiveness of chlorpromazine is scarce, the existing information is generally reassuring and the use of chlorpromazine for NVP is considered safe if used occasionally and in low doses (184, 185, 187). Chlorpromazine is included in the Norwegian guidelines from NGF (34), despite not being currently marketed in Norway. Hence, in practice it is mostly used in hospitals through application. The recommended dosage of chlorpromazine according to Norwegian guidelines is 10 mg two to three times daily administered as tablets or as 25 mg in a 1000 ml 5% glucose intravenous infusion administered over 24 hours (34).

Common side effects of the dopamine antagonists in the phenothiazine group and metoclopramide are sedation and extrapyramidal symptoms, including dystonias and a risk of tardive dyskinesia (46, 188). In June 2013, the European Medicines Agency (EMA) issued a recommendation to change the use of metoclopramide due to a risk of serious neurological adverse events, such as extrapyramidal symptoms, including irreversible tardive dyskinesia (189). As a consequence, it was recommended to restrict the use of metoclopramide to maximum five days duration, with a maximum daily dose of three administrations of 10 mg (189). As five days' treatment is seldom long enough to treat NVP, this change will probably limit metoclopramide's role in the treatment of this pregnancy complaint. The consequence is that pregnant women are deprived of a commonly used agent that is currently known to be safe for the foetus when used during pregnancy, and women are left with fewer agents available for treatment of NVP. The FDA recommends a maximum duration of three months (190). Tardive dyskinesia, which is the most feared adverse effect, is an extrapyramidal disorder characterised by potentially disfiguring and irreversible involuntary movements (191). According to a review from 2010, the risk of tardive dyskinesia is likely to be less than 1% (191). Although female gender has been associated with an increased risk of developing tardive dyskinesia, tardive dyskinesia is generally associated with advanced age (above 60 to 70 years of age). However, young adults, especially girls aged 12 to 19 years, were also identified as having a higher risk of tardive dyskinesia (191), although the absolute risk of developing neurologic side effects of metoclopramide when used during pregnancy for NVP is not known.

5-HT$_3$-antagonists

Ondansetron is a selective serotonin $5HT_3$ receptor antagonist. $5HT_3$ receptors occur in the peripheral nervous system, and in the brain in the CTZ (46, 47). Ondansetron has become a commonly used agent against NVP. A large US study of medication use during pregnancy reported that ondansetron was used by nearly 3% of the women

reported from the centres in Boston and Philadelphia during the period 2003 to 2008 (192).

Questions have recently been raised about the safety of ondansetron (193). Two Danish studies based on the Danish prescription register showed conflicting results with respect to the risk of malformations of the heart (194, 195). One of the studies detected an increased risk of heart defects in offspring (OR 2.0, 95% CI 1.3–3.1) (194). However, this result is derived from an abstract, as no full article has been published yet. The other study, published in the New England Journal of Medicine, did not detect any increased risk of congenital malformations, miscarriage, low birth weight or being small-for-gestational-age (195). A Swedish study, which included 1349 infants exposed to ondansetron during early pregnancy, detected a modestly increased risk of cardiovascular defects (OR1.62, 95% CI 1.04–2.14) and cardiac septum defects (RR 2.05, 95% CI 1.19–3.28) (196). An increased risk of isolated cleft palate (OR 2.37, 95% CI 1.18–4.76) was found in a smaller study that included 55 first trimester exposures (197). Hence, it is recommended to avoid use before pregnancy week 10 (45).

A double-blind randomised controlled trial reported ondansetron to be superior to doxylamine in combination with pyridoxine for the management of NVP (198). However, this study did not use the delayed release form, and it used half the recommended dose of the doxylamine-pyridoxine combination, which may have favoured ondansetron (199). Another randomised controlled trial found that ondansetron and metoclopramide have similar effects on NVP (177).

The recommended dosage of ondansetron in the Norwegian guidelines is 4–8 mg two times daily as tablets, or 4 mg two times daily administered as an intramuscular injection (34).

Common side effects are headaches, constipation and drowsiness (31, 188). Serotonin syndrome is a possible side effect of ondansetron if combined with other medicines affecting serotonin levels, such as selective serotonin reuptake inhibitors (31, 193). The

FDA raised concerns in 2011 suggesting that ondansetron could cause QT prolongation, which can lead to Torsade de Pointes (200). Electrocardiogram (ECG) monitoring is therefore advised in patients with electrolyte abnormalities, which will include many patients presenting with severe NVP/HG (193).

Glucocorticoids

It has been known for more than 30 years that corticosteroids are effective against chemotherapy-induced nausea and vomiting (115), and they are also mentioned in most guidelines for NVP (27, 29-35). The mechanism of action is elusive, and there is conflicting evidence with respect to their effectiveness against NVP (31, 201, 202). Ideally, glucocorticoids should only be used after pregnancy week 10 due to associations between glucocorticoid use and a slightly increased risk of oral clefts when administered before this time point in pregnancy (203-206). They are therefore referred to as last line treatment, and it is recommended that they be reserved for refractory cases of NVP (27, 29-32, 34, 35).

1.7.4 Intravenous hydration and enteral and parenteral nutrition

Patients who are dehydrated and unable to maintain adequate normal electrolyte levels should be rehydrated with intravenous fluid containing the appropriate electrolytes and vitamins (31). It is important to delay glucose infusion until after thiamine has been administered due to concerns about Wernicke's encephalopathy (34).

Refractory patients not responding to pharmacological interventions and who have weight loss are assessed for enteral or parenteral nutrition (31, 34). Enteral nutrition (nasogastric or nasojejunal tube feeding) is preferred to parenteral nutrition since total parenteral nutrition requires a central venous access device that is associated with increased risk of serious complications, such as infections or thrombosis (31, 34, 207). However, partial parenteral nutrition can be administered via a peripheral vein over a

short time period in conjunction with the correction of fluid and electrolyte disturbances, or upon initiating nasogastric or nasojejunal tube feeding (34).

1.7.5 Adjunct therapies

Antacids

Heartburn and reflux symptoms are very common in pregnancy, affecting 40–85% of pregnant women, and have been found to be associated with increased severity of NVP (155). Moreover, adding antacids to the existing antiemetic regimen has resulted in a reduction in NVP severity (208). Consequently, women who experience symptoms such as burping, belching, nausea at night, burning, indigestion or feelings of a lump at the back of the throat may find relief in recommendations that focus on decreasing acid symptoms, such as avoiding high fat or fried foods, sleeping in an elevated position or adding antacids therapy as needed (45). The antacid recommended in the Norwegian guidelines is omeprazole 20 mg once daily (34). UpToDate recommends H_2-receptor antagonists, such as ranitidine, for heartburn and reflux symptoms (31). H_2-receptor antagonists and proton pump inhibitors have been investigated for their safety when used during pregnancy, with reassuring results (209, 210).

A summary of the treatment recommendations described above is shown below in form a suggested treatment algorithm (Figure 3).

Figure 3. *Treatment algorithm for NVP. Adapted from the Norwegian guidelines issued by NGF, UpToDate, Motherisk and the Danish HG guidelines issued by the Danish Society for Obstetrics and Gynaecology (29, 31, 34, 163).*

Abbrevations: PUQE, Pregnancy-Unique Quantification of Emesis; CAM, Complementary and alternative medicine; PO, per os; IM, intramuscular; IV, intravenous; ECG, electrocardiography.

1.7.6 Counselling and emotional support

The Canadian guidelines suggest that support and understanding from close friends and family, and also supportive counselling, may be beneficial for women suffering from NVP (30, 45). One study found a positive association between NVP and stress, and an inverse relationship between stress and social support, indicating that severe NVP associated with perceived stress levels may be mediated by social support (211). Having high social support has been found to be associated with lower severity of NVP (79). Telephone counselling had a positive effect on perceived social support among women with NVP (212). Moreover, a study investigating the impact of professional support, such as including individualised health education and supportive phone calls about NVP, found that the intervention group had significantly lower severity of NVP and perceived level of symptom distress, while showing an improvement in quality of life, when compared to the control group (213).

The importance of taking a woman presenting with NVP seriously has been stressed by several authors (95, 214-217). A high level of patient satisfaction has been associated with women's perceptions that physicians believed in their descriptions of their symptoms (215). A low level of belief in the women's description of the severity of symptoms may result in delayed intervention, and can thereby affect the time required for recovery (215). This experienced lack of understanding of NVP among healthcare personnel was also reported by Locock et al. (216).

1.8 Prevalence of treatment of NVP

Estimating the prevalence of treatment of NVP in prior studies is challenging due to a wide range of definitions of NVP treatment. Treatment of NVP includes both prescription medicines and over-the-counter (OTC) medicines as well as CAM, and the medicines used are not restricted to one ATC class, which means that drug utilisation in pregnancy studies in general seldom provide data on this.

Studies are available from various countries, but the data sources used vary and the study designs have been based on different populations, see Table 3. Studies report the proportion of women taking one or more antiemetic medicines, ranging from 1–3% in the UK, to 14–61% in Canada, with 3% in the Netherlands, 5% in Sweden, 5–10% in Italy, 11–15% in the USA, 11% in Germany, 15%–21% in France, and 26% in Australia in between (52-54, 94, 166, 197, 218-222), see Table 3. However, direct comparison is impossible with such large differences in methodology.

The same challenge applies when considering CAM used against nausea. In addition to a variety of methodologies used, different therapies have been included in the definition of CAM. The proportion of women using non-pharmacological therapies for NVP has been reported to be 1.5% (herbs) / 2.1% (homeopathy) in Germany, 42% in Australia and 18–69% in Canada (52, 54, 94, 219, 223, 224), see Table 3.

Though not specifically reporting prevalence of NVP treatment, two comparative studies of interest is found of which both are indicating a presence of intercountry variations of type and prevalence of NVP treatment. In 1998 an informal survey enquiring about 1st, 2nd and 3rd choice treatment for NVP was conducted in several European countries (225). This study detected wide variations in the types of treatment used against mild and moderate nausea and vomiting, whereas hyperemesis gravidarum was treated quite similarly in the vast majority of countries (225). Another study among women having experienced HG found intercountry variations of frequency of different treatments used against this illness (226). However, in conclusion we have little knowledge about differences in NVP treatments, i.e. conventional and herbal medicines, across countries, and in Norway.

Table 3. *Overview of studies conducted between 2000 and 2014 estimating the prevalence of treatment against NVP.*

Study	Country	Data source	Women included	Use of anti-emetics	Use of other therapies/comfort measures	Maternal characteristics predicting use of medicines
Berard and Sheehy 2014 (221)	Canada	Administrative databases linkage	Pregnant women	13.7% (prescribed medicines)	/	/
Anderka et al. 2012 (197)	USA	The National Birth Defects Prevention Study	Women with NVP	15.4% (incl. herbs)	/	Ethnicity, BMI, study site, year of delivery
Naumann et al. 2012 (220)	USA	A prospective study of gallbladder disease in pregnancy	Pregnant women	10.7%	/	/
Lacasse et al. 2008 (94)	Canada	A prospective observational study of pregnant women receiving prenatal care at a clinic	Women with NVP	20.4%	17.9% non-pharmacological methods	/
Markl et al. 2007 (219)	Germany	German statutory sickness fund	Pregnant women	11.2%	1.5% herbal product 2.1% homeopathy	Social status, age
Hardy et al. 2006 (218)	UK	General practice research data base	Pregnant women	1.1% in early pregnancy and 3.1% in late pregnancy (prescribed for nausea and vertigo)	/	/
Asker et al. 2005 (166)	Sweden	Swedish Medical Birth Registry	All pregnant women	4.5%	/	Education, age parity

Chandra et al. 2003 (54)	Canada	Women calling an NVP Healthline	Women With NVP	43.6%	32.4% non-pharmacological methods	/
Hollyer et al. 2002 (223)	Canada	Motherisk Program NVP line	Women with NVP	/	61.2% CAM	/
Mazzotta et al. 2000 (53)	Canada	Women calling an NVP Healthline	Women with NVP	60.5%	/	/
Mazzotta et al. 2000 (224)	Canada, but recruiting both Canadian and American women	Women calling an NVP Healthline	Women with NVP	Canada: 69.3% USA: 48.5%	Canada: 6.5% USA: 5.1%	
Smith et al. 2000 (52)	Australia	Volunteers for a randomised controlled trial evaluating the role of acupuncture in early pregnancy	Women with NVP	26%	42% other e.g. ginger, naturopath, relaxation sucking sweets	/
DeVigan et al. 1999 (222)	France, UK, Italy, the Netherlands	Women enrolled in the EUROCAT study as controls.	Pregnant women	France/Paris and Bouches-du-Rhône: 20.9% and 15.0% UK: 2.9% Italy/ Emilia-Romagna and Toscana: 5.1% and 10.0% The Netherlands: 2.3%		

Abbreviations: BMI, Body mass index; CAM, Complementary and alternative medicine; EUROCAT, European Surveillance of Congenital Anomalies; NVP, Nausea and vomiting during pregnancy

1.9 Methodological aspects

1.9.1 Pharmacoepidemiology

The medications market is constantly changing. Each year new medicines are marketed, while others are withdrawn and medicines previously only available on prescription become available OTC. Guidelines for the specific disorders may also change. Drug utilisation studies are therefore needed to understand how drugs are used in a defined population, time trends of use and how various factors influence use. Drug utilisation is defined by the World Health Organization (WHO) as 'the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences' (227). Drug utilisation research can be divided into descriptive and analytical studies, and it is an essential part of pharmacoepidemiology, since it describes the extent, nature and determinants of drug exposure (227). The findings from drug utilisation studies form the basis for analytical pharmacoepidemiological studies (227).

Pharmacoepidemiology has been described as 'the study of the use of and the effects of drugs in large numbers of people' (228). It is a research field linking clinical pharmacology and epidemiology (228). The field borrows its focus of inquiry from clinical pharmacology and its methods of inquiry from epidemiology (228).

Since pregnant women are generally excluded from clinical trials due to ethical considerations and concerns about potential teratogenic effects, epidemiological methods are necessary to gather and evaluate information about the population actually using a drug in order to examine its safety of use during pregnancy (228).

Various types of observational epidemiological study designs exist that can be classified as descriptive or analytical (228). An observational study design refers to case reports, case series, analyses of secular trends, case-control studies and cohort studies (228). Case reports, case series and analyses of secular trends are referred to as descriptive studies, while case-control studies and cohort studies are referred to as analytical studies (228). Cohort studies and case control studies represent the two

main types of epidemiological studies (229). These studies provide information about the extent of the association between exposures during pregnancy and the outcomes. They are 'analytical' in their ability to determine measures of association, and can be of a retrospective or prospective design (228). Cohort studies are known as the archetype of epidemiological studies and involve measuring disease within one or more cohorts (229). This design has many advantages, such as enabling incidence rates or risks to be calculated (229). Cohort studies are useful when studying many outcomes and uncommon exposures (228). The exposure data are unbiased, and selection bias is less likely (228). However, cohort studies are not suitable for rare outcomes, they are usually expensive and can take years to complete (228). Furthermore, outcome data may be biased (228).

Cross-sectional studies collect data at a single time point and provide snapshots of the population status with respect to disease or exposure status (229). This design provides rapid answers, and data on all variables are collected once. Multiple outcomes and exposures can be studied, and prevalence estimates can be obtained (229). However, since risk or rate calculations require information across a time period, a cross-sectional study cannot measure disease incidence, and it cannot provide information about causes of disease (229). Nevertheless, cross-sectional studies are useful for descriptive analyses and for raising hypotheses, and for shedding light on problems related to the use of medicines in the population.

1.9.2 Qualitative research design

The social world in the healthcare sector cannot be solely explained by numbers, which may explain the growing interest in qualitative methods among healthcare researchers in recent decades (230). While quantitative research primarily involves numbers, qualitative research focuses on the meanings that are attached to people's experiences of the social world and how that world makes sense to them (230). Qualitative studies are typically used to answer 'why' and 'how' questions, and to explore processes and patterns in people's thoughts and behaviour (231). Quantitative and qualitative approaches complement each other and are increasingly being used

together and in parallel in health research (230). Qualitative research can also be helpful in validating quantitative research results, by providing a different perspective on the studied social phenomena, providing insight to aid the interpretation or understanding of quantitative data, and/or to explain relationships between variables (230, 231). And vice versa, quantitative research can also be used to follow up qualitative research by quantifying the findings of a qualitative study (230).

Various qualitative research methods exist, including direct observation, interviews and text or document analysis (230), of which interviews are most commonly employed in health research (231). Interviews can be conducted as face-to-face interviews with individual respondents or with a group (e.g. focus groups), according to an unstructured, a semi-structured or a structured interview guide (231). It is important that the research design is appropriate to the research question (232).

High quality is also striven for in qualitative research. However, the well-known criteria used to assess the quality of quantitative research – reliability and validity – seem to have an uncertain place in qualitative research (233). The philosophical beliefs underpinning quantitative and qualitative methodologies are traditionally based on different ontologies (232). Hence the criteria applied in quantitative research to assess quality cannot easily be transferred to and applied in a qualitative research setting (232). The general ontological assumption among qualitative researchers is that reality is dynamic, contextual, socially constructed and dependent of time and place. This implies that, in order to study the social world, other more suited theoretical perspectives and methods are needed (232). Though there is agreement that a rigorous application of the principles of qualitative methodology must be striven for at all stages of the research process, there is still an ongoing debate among qualitative researchers on how to handle the traditional concepts of reliability and validity, as well as what criteria to apply when evaluating qualitative research (232, 233). While some believe that reliability and validity should be standards for assessing the quality of qualitative research, this is rejected by others who argue that other terms or concepts are needed (232-234). Denzin and Lincoln suggest replacing

the traditional criteria of internal and external validity, reliability and objectivity with the terms credibility, transferability, dependability and confirmability (see Box 2) (232, 233).

Box 2. *Commonly applied criteria to assess the quality of quantitative and qualitative research. Adopted from Devers (232).*

Quantitative research	*Qualitative research*
Internal validity: The degree to which the findings correctly map the studied phenomenon.	*Credibility:* The 'truth' of the findings, as perceived by the participants and within the context in which the research is carried out.
External validity: The extent to which the results can be generalised to other settings similar to the one in which the study was conducted.	*Transferability*: The extent to which the findings generated are applicable/transferable to other settings with a similar context.
Reliability: The degree to which the findings can be replicated by another researcher.	*Dependability*: The extent to which the research would produce similar or consistent findings if carried out as described.
Objectivity: The extent to which the findings are free from bias.	*Confirmability*: Evidence that verifies the findings must be provided by the researcher.

To conclude, findings from qualitative studies have limitations with respect to the quantitative concept of 'generalisability'. However, the objectives of qualitative research are, as stated above, more to explore and explain in-depth various phenomena than to test the extent to which characteristics apply to a large population (218). To summarise, regardless of qualitative and/or quantitative tradition, an open and detailed description of the research process is important for the reader to be able to assess the quality of the research results.

2. **Aims of the studies**

The overall aim of this research project was to explore various aspects of treatment of NVP with special focus on attitudes to and use of pharmacological treatment. The specific aims of each study were:

Paper I

The primary aim of this study was to investigate whether exposure to ginger was associated with an increased risk of congenital malformations. The secondary aim was to investigate the effects of ginger use on vaginal bleeding, stillbirth/perinatal death, birth weight, preterm birth and Apgar score.

Paper II

This study aimed to describe differences in self-reported nausea during pregnancy, as well as the patterns of use of both conventional and herbal medicine across countries in Western, Northern and Eastern Europe, North America, and Australia. The study also aimed to investigate factors related to nausea and its treatment, as well as the relationships between different self-reported comorbidities and nausea.

Paper III

The aim of this study was to explore thoughts and attitudes among Norwegian pregnant women and GPs about the treatment of NVP, and to identify potential barriers to optimal care for women with NVP.

Paper IV

In aim of this study was to investigate the treatments used for NVP according to NVP severity defined by the PUQE scale among women in Norway. A secondary aim was to assess whether maternal characteristics and attitudes were related to the use of pharmacological treatment of NVP.

3. **Material and methods**

Design, setting and participants

Table 4 provides an overview of the design, setting and participants in the studies that are included in the thesis. A brief description of each study follows below. For further details, please see Paper I−IV.

Table 4. *Overview of the studies that are included in the thesis and their characteristics.*

Paper	Design	Setting	Population/informants
I	Population-based cohort study	Norway	Norwegian pregnant women were recruited at 17-18 weeks of gestation, n = 68,522
II	Cross-sectional study	Multi-national	Pregnant women and new mothers with a child <1 year of age, n = 9,113
III	Focus group discussions	Norway, Bergen	Pregnant women were recruited when attending routine ultrasound examinations, n = 10. General practitioners under specialisation were recruited through contacting supervisors of the educational groups, n = 10.
IV	Cross-sectional study	Norway	Pregnant women or new mother with a child <1 year of age who had experienced NVP, n = 712.

3.1 Paper I The MoBa study: Safety of ginger use in pregnancy

3.1.1 Data sources

The Norwegian Mother and Child Cohort Study

The Norwegian Mother and Child Cohort study (MoBa) is a population-based cohort study conducted by the Norwegian Institute of Public Health, which recruited pregnant women in Norway between 1999 and 2008 (235, 236). The aim of the study is to identify causes of serious diseases in mothers and children (235). Participants were recruited by postal invitation received together with the routine ultrasound

examination offered to all pregnant women in Norway in pregnancy week 17–18. An information brochure, an informed consent form, and the first questionnaire were enclosed with the invitation (235). The recruitment started in the county of Hordaland in Western Norway in 1999, and expanded gradually to include 50 out of 52 hospitals in Norway with more than 100 births annually. In 40.6% of the pregnancies, the women agreed to participate. The last child in the cohort was born in 2009. The cohort now includes more than 90,000 pregnancies and 100,000 children from all over Norway, and the children are still followed (237).

Self-administered questionnaires form the basis for the study. The participants completed two self-administered questionnaires during pregnancy, and one questionnaire when the child was six months old, providing information relevant to this study (238-240). The women completed an additional questionnaire at pregnancy week 22 that covered dietary information (241), but this questionnaire was not used in this study. The first questionnaire was completed during pregnancy weeks 13-17 and covered the period from six months prior to pregnancy until completion. The second questionnaire was completed at pregnancy week 30. The third questionnaire was distributed when the child was six months old, providing information on the last part of pregnancy. The self-administered questionnaires provide information about sociodemographic characteristics, outcomes of previous pregnancies, medical history, maternal health, lifestyle habits, drug exposure and other exposures during pregnancy.

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN), established in 1967, is based on compulsory notification of all live births, still births and induced abortions after gestational week 12 (after gestational week 16 up to 2002), and encompasses all births in Norway (242, 243). The notification form includes information about maternal health prior to and during pregnancy, medicine use during pregnancy, birth complications and interventions, postpartum complications, and the health of the neonate (243-245). Diagnoses are coded according to the International Statistical

Classification of Disease (ICD) and related health problems and unique codes developed by the MBRN (43, 246).

3.1.2 Study population
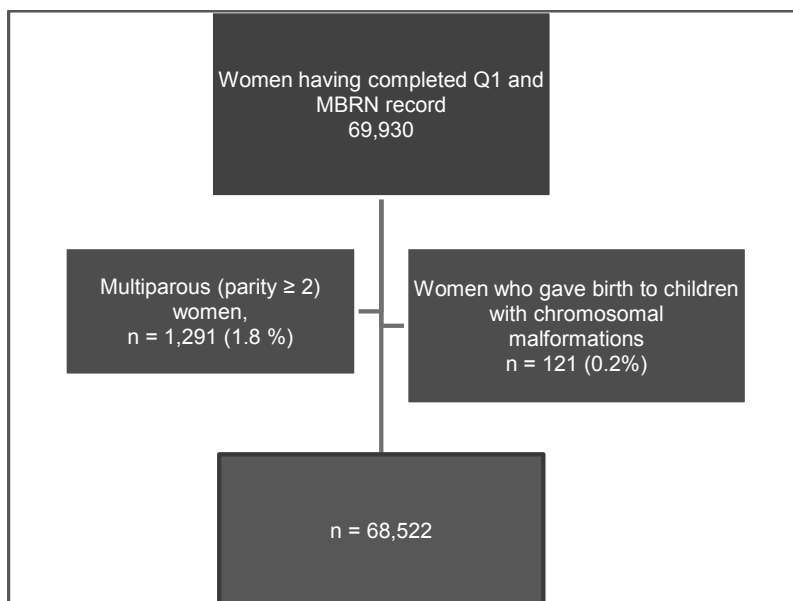
Figure 4. *Flow chart of study population included in the study in Paper I.*

The MoBa quality-assured data file released for research, version 4, was used in this study. Women who both have a record in MBRN and had answered the first questionnaire were included in the study. Women who gave birth to multiples or to children with chromosomal malformations were excluded. Hence, the final study population included 68,522 women and their infants.

3.1.3 Measures

Information about ginger use was retrieved from the three MoBa questionnaires (238-240). Several indications were mentioned in the questionnaires and, for each indication mentioned, it was possible for the women to specify several products used for the complaint. Additionally, the women could report the use of supplements and herbal products in response to specific questions about such use. The use of herbal products was reported as names of products in free text fields. The research team

systematically reviewed all medicine text fields and text fields for dietary supplements/herbal remedies in the three questionnaires for herbal products. All identified herbal products were systematically coded according to a pre-determined herbal classification list based on the herbal ingredient(s). This classification system was developed by the research team and included the common name of the herb and a seven-character specific code to facilitate standardisation of the coding in the questionnaire database. This work took the research team more than a year and included 1) sorting each text field by product/herbal name in descending order to make sure that no herbal product was missed, and 2) creating a classification list and making sure that the individuals involved coded the herbals in the same way.

Information about outcome variables was retrieved from MBRN, with the exception of information about maternal vaginal bleeding, which was self-reported and retrieved from MoBa. We investigated all malformations as defined by the MBRN, which follows the European Surveillance of Congenital Anomalies' (EUROCAT) classification system of congenital anomalies (246, 247). Malformations were classified as all malformations, major malformations and cardiovascular malformations. A patent ductus arteriosus (ICD-10 code Q25.0) in premature infants was not considered a cardiovascular malformation (43). We also investigated the following adverse pregnancy outcomes: stillbirths and perinatal deaths, low birth weight, preterm birth, and low Apgar score at five minutes after birth.

The detailed nature of the MoBa questionnaires in combination with information from MBRN provided information on a wide range of potential confounding factors.

3.1.4 Statistical analyses

Pearson's chi-square test was applied to test for associations between ginger use and maternal characteristics or variables related to maternal illness. A p-value <0.05 was considered significant. To investigate the risk of malformations and selected pregnancy outcomes associated with ginger use, univariate and multivariable logistic regression analyses were used to obtain crude and adjusted odds ratios (ORs), respectively. Statistically or clinically significant variables were explored for each

pregnancy outcome. The selection of variables to be included in the potential confounder sets was based on theoretically potential influences, as well as the results from exploratory data analysis. Maternal age, parity, pre-pregnancy body mass index (BMI), folic acid use, smoking, education, NVP, previous miscarriages/stillbirths, year of delivery, and infant sex were considered possible confounders, and adjusted for when estimating the risk of malformations and preterm birth. The remaining selected pregnancy outcomes were also adjusted for by length of gestation.

3.1.5 Ethics

The MoBa study was approved by the Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate.

3.2 Paper II The multinational web-based cross-sectional study: Treatment of NVP

3.2.1 Data source and study population

The multinational cross-sectional study among pregnant women and new mothers

Paper II was a sub-study using data from a web-based, cross-sectional study carried out in 18 countries simultaneously. An online self-completed questionnaire was available for two months in each participating country between 1 October 2011 and 29 February 2012. The national coordinators in each of the participating countries chose relevant, commonly visited pregnancy and baby-related websites on which an advert containing a link to the questionnaire was posted (15). The questionnaire was originally developed in English and Norwegian, and was translated into the relevant languages. The quality, comprehension and adaptation of the translated questionnaire to the relevant national context were assured by the national coordinator in each participating country. Women who were pregnant or who had a child of <1 year of age could participate in the study.

In order to assess the representativeness of the study population, the sociodemographic and lifestyle characteristics (i.e. age, marital status, education and

smoking) of the study population were compared to the general birthing population in the corresponding country. The similarities were satisfactory, with the exception that the study participants were generally more educated than the general birthing population (15). In specific countries (Australia, Canada, France, the Netherlands, Russia and the USA), the study sample constituted a small proportion of the general birthing population (15).

The original data file comprised 9,459 women from the 18 participating countries who completed the online questionnaire, including 346 women from various countries in South America who accessed the questionnaire via North American websites. The women from South America were omitted due to a risk of being a biased group. Hence, the final study population consisted of 9,113 women.

3.2.2 Measures

Information about self-reported nausea and other health disorders/short-term illnesses during pregnancy was available from the questionnaire, together with information about treatments used for these complaints. Standardised questions about OTC use were also posed to the women, as well as questions about herbal medicine use during pregnancy. Medicines were defined as single products containing one or more active ingredients, and were coded into the corresponding ATC codes according to the WHO ATC index (173). Supplements such as vitamins, minerals and CAM, were distinguished from medicines and coded separately.

Symptoms of depression were measured by the Edinburgh Postnatal Depression Scale (EPDS). This is a self-rating scale consisting of ten items, developed by Cox et al. to detect postnatal depression (248). Though it was initially developed to detect postnatal depression, the scale has also been validated as a screening tool for major depression in pregnant women with satisfactory results, and it has been used in several studies worldwide (249, 250). Cut-off scores of 11, 10 and 10 applied at weeks 12, 24 and 36 of pregnancy, respectively, resulted in 79%, 70% and 76% sensitivity, respectively, and 97%, 96% and 94% specificity, respectively (250). The scale rates the intensity of depressive symptoms over the previous seven days, and

each item is scored 0, 1, 2 or 3, resulting in a total score range between 0 and 30. Validated translated versions of the original EPDS were available in Dutch, French, German, Icelandic, Norwegian, Slovenian, Spanish and Swedish (249). For the remaining languages, translated versions used in previous studies were applied (251-254), except for the Slovenian version, which was developed by two independent linguistic experts. We used a cut-off of ≥13.

In addition, detailed information about maternal sociodemographic and lifestyle habits was retrievable from the questionnaire.

3.2.3 Statistical analyses

Descriptive statistics were used to calculate the prevalence of conventional and herbal medicine use against nausea during pregnancy. Univariate and multivariable generalised estimating equation (GEE) analyses were used to explore potential significant associations between maternal characteristics and the use of conventional medicines against nausea, and between comorbidity and nausea and its treatment. The GEE with the binary logistic model was applied to correct for clustering on region of residency. Crude and adjusted ORs are presented with 95% confidence intervals. Reduced models were fit by excluding non-significant variables unless removal of the variable caused a >10% change in the effect estimate.

3.2.4 Ethics

The study was approved by the Regional Ethics Committee, Region South-East in Norway. In addition it was notified to and approved by each of the relevant national Ethics Boards when required by national legislation. Answering 'Yes' to the question 'Are you willing to participate in the study?' after having been shown the study description was regarded as giving informed consent.

3.3 Paper III The focus group discussion: Attitudes to and thoughts on treatment of NVP among pregnant women and general practitioners

3.3.1 Study population

Women attending a routine ultrasound examination in pregnancy week 17–18 at Kvinneklinikken, Haukeland University Hospital, and who had experienced NVP during their current pregnancy, were handed an information brochure that included an invitation to participate in a study by healthcare professionals working at the clinic. The information pamphlet contained information about the study as well as contact details for the research group. The women were kindly asked to get in touch if they had any questions or were interested in participating in the study. Due to slow recruitment, the snowball recruitment method was also applied. In total, 10 pregnant women were recruited and grouped into two focus groups of four and six participants, respectively.

Educational groups for GPs under specialisation in general practice were contacted by e-mail with the aim of recruiting GPs to the study. Two focus group discussions were carried out with five GPs in each group.

3.3.2 Measures/information

The women and the GPs were asked to tell about their own thoughts and experiences of treatment of NVP. Elements included in the interview guides are shown in Table 5.

Table 5. *Elements included in the interview guides.*

Pregnant women	General practitioners
Experience of NVP	Thoughts about treatment
	Important concepts in the care of
Different aspects of treatment	pregnant women with NVP
- Where to seek advice	The question of treatment
- The question of treatment	- Thoughts about treatment
- Thoughts about dietary and lifestyle changes	- Thoughts about dietary and lifestyle changes
- Thoughts about medicines	- Thoughts about medicines
- Thoughts about alternative treatments	- Thoughts about alternative treatments

3.3.3 Data collection

Data collection was carried out as part of two master's projects. Two separate interview guides of a semi-structured nature containing open-ended questions were developed for the focus group discussions with the women and the GPs. The focus group discussions were audio-recorded and moderated by the master's student, who also transcribed the audio-recordings verbatim with one exception; in this case the role of the moderator was filled by the student's supervisor, who quality-checked the verbatim transcription. The PhD student acted as secretary.

The focus group discussions lasted approximately 60 minutes each.

3.3.4 Analysis

The transcripts from the focus group discussions with the GPs and the pregnant women were analysed separately, and according to the principles of systematic text condensation as described by Malterud (255). Firstly, to establish an overview of data, the transcripts were read as a whole by three of the members of the research team who had also been present at the focus group discussions. Secondly, preliminary themes, representing different aspects of the participants' thoughts on and attitudes to treatment of NVP were identified by each member of the research team individually.

The members of the research team then met, and agreed on themes or code groups through collaborative negotiation. Thirdly, meaning units (a text fragment that contains information about the research question) were sorted under the appropriate themes or code groups. The content of the coded groups was then reduced to a condensate that aimed to capture the essence of the meaning units. Lastly, descriptions and concepts were developed based on the condensates.

3.3.5 Ethics

The study was approved by the Regional Committee for Ethics in Medical Research, Region West, and the Norwegian Data Inspectorate.

3.4 Paper IV The Norwegian web-based cross-sectional study: Treatment of NVP

3.4.1 Data source and study population

The EMESIS study

This study is based on a cross-sectional study that collected data through an online questionnaire accessible from 10 November 2014 to 31 January 2015. A link to the questionnaire was posted on websites and social networks commonly visited and consulted by pregnant women and/or new mothers. It was also accessible via the study's own Facebook page. A pilot study was carried out (n=5), resulting in only minor changes to the questionnaire. Collected data were scrutinised to uncover potential duplicates (based on sociodemographic data), without detecting any.

Women who were pregnant or who had a child of <1 year of age, and who had experienced NVP in their latest pregnancy, were eligible to participate.

3.4.2 Measures

The questionnaire provided data on maternal characteristics, NVP and treatments used for NVP, such as conventional medicines, CAM and hospitalisation. The questionnaire also included questions on the women's beliefs about medicines and

alternative treatments. A list of commonly used therapies was presented to the women, who were asked to report the therapy used, duration of therapy, dosage and who initiated the treatment.

The PUQE scale was used to measure symptoms of NVP and classify the women into three groups according to the severity of their symptoms (44). They were asked to report on the extent of their NVP during a typical 24 hours in the period with the most severe symptoms. PUQE consists of three items assessing the severity of symptoms; the numbers of hours of nausea, the number of episodes of retching and the number of episodes of vomiting within the last 24 hours (see Box 3). Each item is scored from 1 to 5 points. The PUQE score is calculated by adding the values from each category, resulting in a total score ranging from 3 to 15 points. A score of ≤ 6 points is classified as mild NVP, 7–12 points as moderate and a score ≥ 13 as severe. PUQE has been validated to correlate with the following factors: risk of hospitalisation due to severe NVP, insufficient nutritional intake, inability to take iron supplements, and reduced well-being/quality of life (256, 257). PUQE was recently translated into and validated in Norwegian (257).

Box 3. *The 24-hour Pregnancy-Unique Quantification of Emesis scale (PUQE-24). Adapted from Ebrahimi* et al. *(44).*

Motherisk PUQE-24 scoring system					
In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
In the last 24 hours have you vomited or thrown up?	7 or more times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	I did not throw up (1)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)

PUQE-24 score: Mild ≤6; Moderate: 7-12; Severe ≥13

How many hours have you slept out of 24 hours? Why?_____

On a scale of 0 to 10, how would you rate your well-being?_____
0 (worst possible), 10 (the best you felt before pregnancy)

3.4.3 Statistical analyses

Univariate and multivariable logistic regression analyses were performed to explore potentially significant associations between maternal characteristics and the use of conventional medicines for NVP. Reduced models were fitted by excluding non-significant variables, unless removal of the variable caused a >10% change in the effect estimates.

3.4.4 Ethics

The participants were presented the study description before completing the questionnaire. If the woman answered 'Yes' to the question 'Are you willing to participate in the study?' this was regarded as giving informed consent. The study was approved by the Regional Committee for Ethics in Medical Research, Region West, and the Norwegian Data Inspectorate.

4. **Summary of results**

4.1 Paper I The MoBa study: Safety of ginger use in pregnancy

In total, 68,522 women were included in the study, of whom 1,020 (1.5%) reported using ginger during pregnancy. We found that 466 women (45.7%) used ginger during the first trimester. NVP was the most frequently reported indication for the use of ginger.

Though women who used ginger during pregnancy were more likely to have experienced vaginal bleeding after week 17 than controls, when the analyses were restricted to vaginal bleeding more than spotting, neither crude nor adjusted ORs revealed a significant association. No association was found between ginger use and vaginal bleeding before week 17.

Use of ginger during the first trimester of pregnancy or at any time during pregnancy was not associated with an increased risk of malformations in general, major malformations, or cardiac malformations, neither according to crude nor adjusted analyses (Figure 5). In addition, no significant associations were detected between the use of ginger during pregnancy and a risk of stillbirth/perinatal death, low birth weight, preterm birth, or low Apgar score in univariate analyses or after adjustments were made (Figure 5). Adjusted ORs are shown in Figure 5.

The following maternal characteristics were associated with the use of ginger: a higher level of education, non-smoking and use of folic acid before and during or only during pregnancy. Compared to the women who did not use ginger, use of ginger was also associated with having experienced any NVP, having been hospitalised during pregnancy due to prolonged NVP, having had NVP during a previous pregnancy, having been on sick leave during pregnancy, and having given birth during the period 2003–2006.
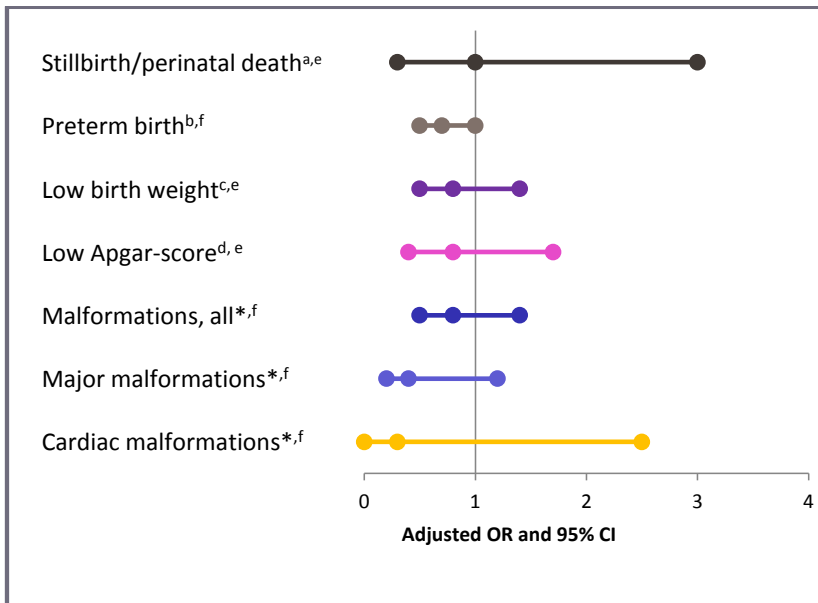
Figure 5. *Associations between pregnancy outcomes and ginger exposure. Adjusted ORs are shown.*

*Ginger exposure during 1ˢᵗ trimester.

Abbreviations: OR, odds ratio; CI, confidence interval

Malformations were defined according to the definitions of the MBRN and International Clearinghouse for Birth Defects.

[a] Includes infants who were stillborn or died during the first 28 days of life (incl. termination of pregnancy).

[b] Includes infants born at a gestational age of <37 weeks, which WHO defines as preterm.

[c] Includes infants with a birth weight of <2500 g, which WHO defines as low birth weight

[d] Includes infants who had an Apgar score of < 7 at 5 min after birth.

[e] Adjusted for maternal age, parity, pre-pregnancy BMI, folic acid use, smoking, NVP, education, previous miscarriages/still births, length of gestation, year of delivery, and infant sex.

[f] Adjusted for maternal age, parity, pre-pregnancy BMI, folic acid use, smoking, NVP, education, previous miscarriages/still births, year of delivery, and infant sex.

4.1.1 Additional sub-analyses of risk of vaginal bleeding stratified by timing of ginger use

The previous analyses on vaginal bleeding and ginger were not stratified by timing of use. Additional sub-analyses are therefore presented in this section. The results of the analyses after stratification by timing of use did not reveal any significant increased risk of vaginal bleeding (unpublished, see Table 6). Adjustments were made for NVP, maternal age, parity, maternal pre-pregnancy BMI, maternal smoking, folic acid use, pervious miscarriages, physical activity and education.

Table 6. Use of ginger and risk of vaginal bleeding stratified by timing of use.

	Total N=68,522 n (%)	Use of ginger Q1 N=834 n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Vaginal bleeding before week 17	13,255 (19.3)	167 (20.0)	1.0 (0.9-1.2)	0.9 (0.7-1.1)
Hospitalised due to bleeding before week 17	203 (0.3)	4 (0.5)	1.6 (0.6-4.4)	1.4 (0.4-4.3)
	Total N=68,522 n (%)	**Use of ginger Q3Q4** N=305 n (%)	**Crude OR (95% CI)**	**Adjusted OR[a] (95% CI)**
Vaginal bleeding in week 17 and after	4,027 (5.9)	23 (7.5)	1.3 (0.9-2.0)	1.4 (0.9-2.2)
Vaginal bleeding in week 17 and after, more than spotting	1,430 (2.1)	9 (3.0)	1.4 (0.7-2.8)	1.7 (0.9-3.3)
Hospitalised due to bleeding in week 17 and after	362 (0.5)	2 (0.7)	1.2 (0.3-5.0)	1.5 (0.4-6.3)

Abbreviations: OR, Odds ratio; Q1, first questionnaire in MoBa completed in pregnancy week 17-18; Q3Q4, third and fourth questionnaire in MoBa, completed in pregnancy weeks 30 and 6 months after giving birth, respectively.
[a] Adjusted for NVP, maternal age, parity, maternal pre-pregnancy BMI, maternal smoking, folic acid use, previous miscarriages, physical activity, education

4.2 Paper II The multinational web-based cross-sectional study: Treatment of NVP

Altogether, 9,113 women were included in the study, the majority of whom were residents of Europe (Western, n=3,201; Northern, n=2,820; Eastern, n=2,342), followed by North America (n=533) and Australia (n=217). A total of 6,701 (73.5%) had experienced nausea during pregnancy. Among respondents with nausea, conventional medicines were used by 1,201 (17.9%) women and herbal medicines by 556 (8.3%) women. The extent of self-reported nausea and its treatment showed geographical variation. Use of treatment of nausea among women experiencing nausea by country of residence is shown in Figure 6.
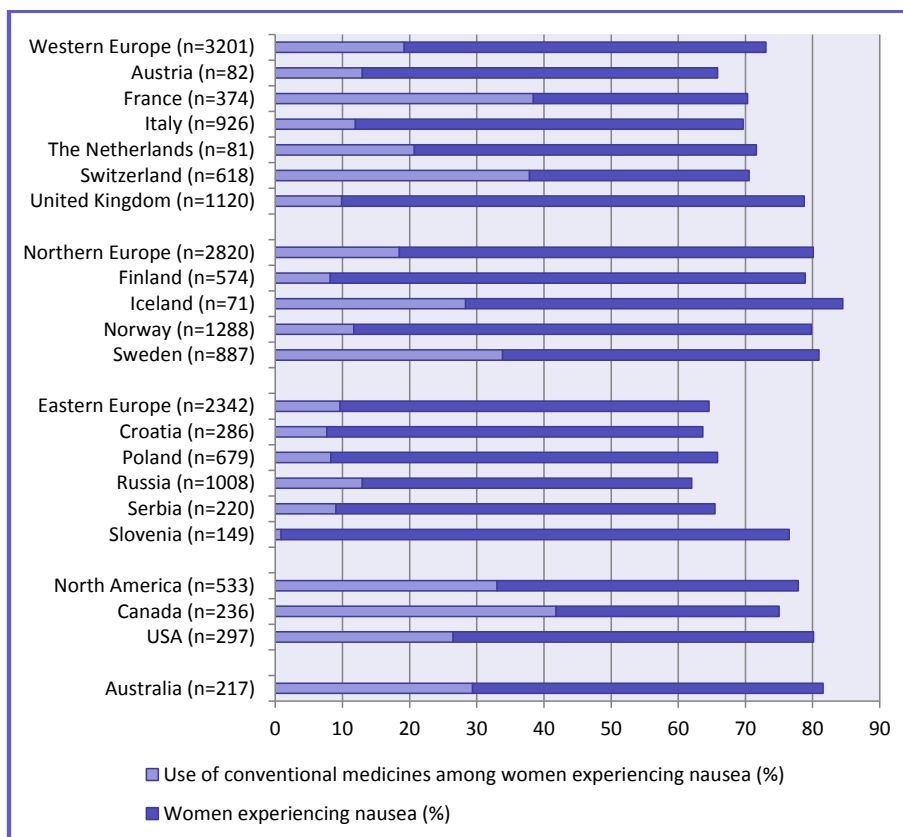
Figure 6. *Use of treatment against nausea among women experiencing nausea by region of residence.*

The prevalence of nausea was lowest in Russia (62.0%) and highest in Iceland (84.5%). The proportion of women using any antiemetic among those with nausea was highest in Canada, France, Sweden and Switzerland. In the majority of the countries, the most commonly used medicines were antihistamines or metoclopramide, except for in the USA (ondansetron) and Russia, Serbia, Croatia and Slovenia (antacids). The most commonly used herbal medicine in the vast majority of countries was ginger. Education, working status and folic acid use were significantly associated with the use of medicines for nausea. Women who reported nausea reported having comorbidities significantly more often, especially heartburn.

4.3 Paper III The focus group discussion: Attitudes to and thoughts on treatment of NVP among pregnant women and general practitioners

Two focus group discussions were held with pregnant women and two with GPs in Norway. Both groups of participants elaborated on several aspects of nausea and pregnancy care. The GPs expressed that it was important to normalise symptoms of NVP. However, the women felt that the GPs trivialised their distress due to NVP, implying that the pregnant women and the GPs seemed to talk at cross purposes. The women missed acceptance and acknowledgment from their GP of how debilitating NVP is to live with. Moreover, the women missed being evaluated properly for the severity of their NVP symptoms. The GPs had a wish for an objective instrument to measure symptom severity.

Though the women had cried out for help due to great distress, they were sceptical about using medicines while pregnant and tried to avoid such use despite being ill. However, the women made it clear that they realised that the choice of treatment was individual and respected others for using any. The choice of treatment seemed to depend on how much one could bear of the negative impact caused by the NVP symptoms. The GPs seemed to be unsure about how to treat NVP when dietary and lifestyle interventions were insufficient. Though medicines were considered to be the next step, the overall attitude among the GPs was to avoid medicines against NVP, mainly due to fear of teratogenicity. Referrals to the thalidomide tragedy were made by both the GPs and the women. The GPs wanted a medicine with NVP as approved indication. A general lack of belief in the effectiveness of the medicines used for NVP was expressed by some of them. Sick leave seemed to be an important part of the treatment regime applied by the GPs, but was also presented as a dilemma with the Norwegian Labour and Welfare administration's strict policy on one side and the pregnant women's begging on the other side. The women had good experience of graded sick leave.

4.4 Paper IV The Norwegian web-based cross-sectional study: Treatment of NVP

Altogether, 712 women in Norway were included in the study. According to the PUQE classification, 62 (8.7%), 439 (61.7%) and 210 (29.5%) had mild, moderate and severe NVP, respectively. A total of 277 (38.9%) women had used one or more antiemetics, 384 (53.9%) women had used CAM, and 188 women had used both conventional medicines and CAM. Severity of symptoms, education and work situation were factors associated with the use of medicines for NVP. The most commonly used medicine was meclizine, closely followed by metoclopramide. The majority of the women using medicines (60.6%) had only used one medicine, although the maximum number of medicines used was six. Among the women who had only used one medicine, only 53.5% had used an antihistamine, which is recommended as first line treatment for NVP. This implies that guidelines are not consistently followed. Ginger and acupressure were the most commonly used types of CAM, which is in accordance with recommendations made in the guidelines. Different drug utilisation patterns were found between the groups of women with different severity of NVP, showing a gradient towards higher use of all medicines for NVP with increasing severity. Nonetheless, many with moderate and severe symptoms did not receive any pharmacological treatment (70.2% and 32.9%, respectively). Of the women who had been on sick leave due to NVP, sick leave was prescribed without initiating medical treatment for 266 (62.1%) women, and only 37 (8.6%) women started medical treatment before they went on sick leave.

The women's beliefs about medicines had an important impact on their use of medicines for NVP. Women who agreed with or were uncertain about the statement 'It is better for the foetus that I use medicines and get well than to have an untreated illness during pregnancy' were more likely to have used medicines than women who disagreed. In total 79.4% reported that they had a higher threshold for using medicines while pregnant, and only 29.6% believed that the foetus would benefit from the mother taking a medicine to get well. Severity of symptoms was associated with the women's beliefs.

5. **Discussion**

5.1 Main findings

Several of our findings provide new knowledge about attitudes to and the treatment of NVP. The most important findings from a clinical perspective are:

The extent of self-reported nausea and its treatment varied by country. In more than half of the countries, treatment rates with conventional medicines were below 20%. In the majority of countries, antihistamines and metoclopramide were the most commonly used conventional medicines, and ginger the clearly most commonly used herbal medicine. Respondents who suffered from nausea also had a high burden of comorbidity. Overall, 74% of women had experienced nausea during pregnancy, of whom 18% had used conventional medicines and 8% had used herbal medicines. (**Paper II**).

In the Norwegian study, we found that many women with moderate and severe symptoms did not receive any pharmacological treatment, 70% and 33%, respectively. Sick leave was prescribed without initiating medical treatment for 62% of the women. The women's beliefs about medicines had an important impact on their use of medicines for NVP. Meclizine, closely followed by metoclopramide, was the most commonly used conventional medicine, while ginger and acupressure were the most commonly used CAM (**Paper IV**).

The use of ginger during pregnancy was not associated with any increased risk of congenital malformations. No increased risk of stillbirth/perinatal death, preterm birth, low birth weight, or low Apgar score was detected for the women exposed to ginger during pregnancy compared to women who had not been exposed (**Paper I**).

The GPs thought it was important to normalise NVP symptoms. However, the women felt their distress due to NVP was trivialised by the GPs. The women were sceptical about using medicines while pregnant, and they tried to avoid such use despite being

ill. The GPs appeared to be uncertain about medical treatment of NVP. They also expressed a lack of belief in the effect of medicines against NVP. Sick leave seemed to be an important part of the treatment regime applied by the GPs (**Paper III**).

Moreover, from an academic perspective, this doctorial work has shown that use of e-epidemiology and the internet enable efficient and unique data collections of high quality. This holds important promise for future studies.

5.2 Methodological considerations

5.2.1 Paper I The MoBa study: Safety of ginger use in pregnancy

The MoBa and MBRN

The MoBa study is exceptional in many ways. This large population-based study includes 95,000 pregnancies, 75,000 fathers and 114,500 children (258). The prospective nature of the data collection largely avoids recall bias and also diminishes the risk of differential misclassification of the exposure, with subsequent limited risk of biased measures of associations (259). Additionally, the vast diversity of information on health-related factors, sociodemographic and lifestyle factors enabled important potentially confounding factors to be controlling for in the multivariate models.

The information in the population-based registry MBRN is also prospectively collected by healthcare personnel during pregnancy and at birth (242). MBRN provides medically confirmed records and is unlikely to suffer from selection bias given its population-based nature.

Response rate, selection-bias and representativeness

MoBa was based on self-selection. Of all the invited women, 40.6% consented to participate in MoBa, introducing a risk of selection bias. Indeed, it has been shown that, when compared to the total Norwegian birthing population, the women in MoBa differ with respect to several exposure and outcome variables (259). The youngest

women, smokers, those living alone, mothers with more than two previous births and with previous stillbirths are underrepresented in MoBa, while women who used folic acid and multivitamins are overrepresented. With respect to pregnancy outcomes, women with stillbirths or neonatal death were underrepresented. Nilsen et al. also examined for differences in association measures for eight well-known exposure-outcome associations between the participants in MoBa and the general birthing population, but no statistically significant relative differences were found (259). The authors therefore conclude that, while these differences have implications for prevalence studies, the indications are that the exposure-outcome associations found in MoBa are valid.

The selection bias, which could indicate that MoBa represents the more healthier segment of the population, could imply a higher prevalence of ginger use in MoBa, since it is found that non-smokers and/or women who use folic acid or multivitamins are more likely to use herbs during pregnancy (14, 260). However, the low prevalence of ginger use detected in MoBa indicates that this was not the case. As regards women experiencing NVP and women who were hospitalised due to prolonged NVP the prevalence found in both cases were similar to what is known from the literature (37).

Information bias, reliability and validity of collected data

Information about maternal sociodemographic, lifestyle characteristics and pregnancy originate from MoBa or the MBRN. Information retrieved from MoBa is dependent on the women's accuracy of recall and reporting. In order to enhance recall and reporting of herbal products in MoBa, indication-oriented reporting of substances was applied. In addition, women were specifically asked in all three questionnaires to give the complete name(s) of all vitamins and dietary supplements they had used, including alternative/herbal remedies and dietary products. The information about ginger use was based on self-reporting which may introduce possible underreporting of use. Indeed, the prevalence of use was found to be of a much smaller magnitude compared to what is found in other studies (17, 123-125). Though these studies, many

of which were specifically designed to study the use of herbal products during pregnancy, may overestimate use due to selection bias, it is possible that the women in MoBa did not comprehend that the intake of herbs in all forms was to be reported. Ginger root can be used in fresh or dried form, in capsules, or prepared as a tincture or a tea. Fresh ginger root or ginger prepared as a tea may not be perceived as a 'medicine'. Furthermore, one third of the reported ginger use was independent of indication. A master's thesis study conducted in Bergen, Norway in 2008–2009, found that the reported use of herbs during pregnancy increased from 35.2% in response to a general question about use of herbal products to 52.8% after asking about the use of ten specific herbs (261).

Moreover, information about dosage and administration was not available in MoBa, which is indeed a limitation. However, estimating the correct dosage is a general problem when studying herbal medicines. Herbal products are seldom standardised. Herbal medicines may contain a large variety of constituents, and if the active component(s) is/are unknown, standardisation is not possible. Moreover, several environmental and genetic factors may affect the complex mixture of constituents (262). Climate, altitude and growing conditions, time of harvesting, which plant parts are used, storage conditions and processing treatments are all factors that can affect the quality and contents of the herbal product, and, consequently, the content may differ from product to product and even from batch to batch (262).

All information retrieved from the MBRN is based on medically confirmed records and is prospectively collected during prenatal care and at birth. This information is therefore unlikely to suffer from recall or information bias. However, the possibility of random underreporting of minor malformations cannot be ruled out.

Sample size and statistical considerations

Power analyses revealed that the statistical power of our data was sufficient to rule out twofold or greater increases in the risk of outcomes that occurred more frequently than in 2% of the study population. For rarer outcomes, such as cardiac malformations, low Apgar score and stillbirth/perinatal death, the statistical power

was 60%, 72% and 50%, respectively. Consequently, even larger studies are needed to have adequate statistical power to rule out an increased risk of rare negative outcomes.

5.2.2 Papers II and IV The multinational and the Norwegian web-based cross-sectional studies: Treatment of NVP

The multinational and the Norwegian study of treatment of NVP shared many of the same characteristics in that they were both web-based surveys aiming to recruit pregnant women and new mothers. These two studies will therefore be discussed together in the following section.

The multinational study of treatment of NVP was based on the Multinational Medication Use in Pregnancy Study. This study was unique in that the data were uniformly collected in the period between 1 October 2011 and 29 February 2012 from over 9,000 women from 18 countries. The Norwegian NVP study was the first of its kind to study the management of NVP according to severity in a Scandinavian country. Data from all over Norway were uniformly collected via the internet.

Using an anonymous, web-based questionnaire was an approach that made it possible to reach a large sample of pregnant women and new mothers from several countries worldwide in the multinational study, and from all over Norway in the Norwegian study. The internet is increasingly used for online surveys and web-based research (263), and web-based recruitment methods have shown reasonable validity in epidemiological studies (264, 265). In various research fields, it has been found that the information reported in web-based questionnaires is of as good quality, equivalent to and as reliable as the information provided on paper (266-268). Furthermore, it was recently shown that information about chronic disorders among pregnant women was validly collected via web-based questionnaires with equal or better quality when compared to obstetric records (269). Electronic entry of data largely enables data entry errors to be avoided.

Response rate and representativeness

Conventional response rates could not be calculated due to the web-based approach that was applied in the two studies. Response rates for web-based questionnaires have been studied, and the latest studies suggest that response rates in web-based studies are increasing, and are sometimes even higher than in paper-based studies (270). However, the response rates in web-based questionnaires seem to depend on the target population, the design and the context (271). Since pregnant women have been shown to be frequent users of the internet and the internet penetration rate is high among women of childbearing age (272-278), it is reasonable for studies targeting the pregnant population to adopt a web-based approach. The representativeness of the Multinational Medication Use in Pregnancy Study was assessed, as previously described in the Material and methods section. The participants were generally more highly educated than the general birthing population.

Although there were slightly fewer smokers, and slightly more women using folic acid before the pregnancy, the study participants in the Norwegian study were reasonably comparable to the general Norwegian birthing population with respect to residential area, age, marital status, folic acid use and smoking status. However, also the participants in this study had a generally higher level of education than the women in the general population.

The higher education of the respondents found in both studies may have had an impact on their choice of treatment. Moreover, with respect to the Multinational Medication Use in Pregnancy Study, the findings for the countries where the study sample only comprised a small part of the general birthing population should be interpreted with caution.

Selection bias

Banners with invitations to participate in the studies were posted on pregnancy and baby-related websites nationally and internationally. Hence, a risk of self-selection bias cannot be excluded. Efforts were made to reduce selection bias, such as

endeavouring to reach a wide proportion of the target population by posting the banners on two to three websites in each participating country in the multinational study. The national coordinators chose the most relevant websites, social networks and pregnancy forums in their respective countries. With respect to the Norwegian study, in addition to posting the banner on commonly visited websites, a link was also posted on a Facebook page specifically created for the study. Studies have shown that the vast majority of pregnant women go online for pregnancy-related information, most commonly visiting social networks and online discussion forums (272, 273). Moreover, the internet penetration rate is generally high among women of childbearing age (274-278). In Norway, 97% of women aged 16-44 use the internet on a daily basis (279). A selection bias with respect to the inclusion of slightly healthier and more educated women could still have occurred. However, this selection bias applies to most epidemiological research based on information collected from individuals. It is not a bias solely associated with studies using web-based approaches (259). There is a possibility, though, that women suffering from nausea may have been more likely to seek information on the internet and, consequently, more likely to participate in the study. Moreover, women suffering from severe symptoms may be more motivated to participate in the study, which could explain the high prevalence of women with severe symptoms in the study population in the Norwegian study. Then again, the most severely affected women will be too sick to participate.

The original data file from the Multinational Medication Use in Pregnancy Study included 9,459 women, 346 of whom were South American women who accessed the questionnaire via North American websites (15). The 346 women from South America were excluded from this current sub-study in an effort to reduce selection bias, as they were considered to be a special group of women. For the same reason, we also included level of education constructing the full multivariate models. However, the possibility that the respondents differ from the general birthing population in ways that our analysis cannot control for cannot be excluded.

Information bias

As the data in these studies are based on a self-completed questionnaire, the information provided is dependent on the women's accuracy of reporting and recall. Hence, a recall bias cannot be excluded. Efforts were made to reduce the risk of recall bias, such as including women with a child of ≤ 1 year of age.

With respect to the multinational study, the prevalence of nausea may have been underestimated due to the inclusion of women at an early stage of their pregnancy, since nausea often does not occur before gestational weeks 6–8. However, this only applies to the 182 women (2.0%) who were less than six weeks pregnant at the time of participation. The fact that we found a prevalence of nausea in line with the prevalence reported in the literature further supports our approach. The questions about use of medicines were indication-oriented, and a list of OTC medication categories together with brand name products was presented to the women in order to aid recall of these medicines. A similar approach was applied in the Norwegian study in which brand name products were presented together with drug name.

In the Norwegian study, severity of symptoms was measured using PUQE (44). However, since maternal reporting of information was retrospective for women not being at the peak of their symptoms, a risk of overestimating the severity of symptoms was introduced. It has previously been demonstrated by Koren et al. that women have a tendency to overestimate the symptoms when reporting retrospectively (280). In an effort to reduce this risk, women whose youngest child was older than one year of age were not eligible to participate, but we cannot rule out this risk completely. However, another study that used the three PUQE questions to assess NVP retrospectively did not find evidence of differential recall when stratified by gestational age (281).

Reliability and validity of data

Nausea as a diagnosis was self-reported, depending on the women's own perception of the complaint and accuracy of reporting, introducing a lack of validity. However,

as nausea is mainly a subjective complaint, self-reporting probably reflects the actual condition quite well.

The EPDS is found to be an instrument with valid psychometric properties, also when administered on the internet (282). In this study, a cut-off score of ≥13 was applied, which is considered to have a high sensitivity (248). However, administration of EPDS at two time points is considered to be more valid than one to avoid detection of transient distress rather than depressive symptomatology (249).

PUQE is a validated tool that has been shown to correlate with risk of hospitalisation due to severe NVP, increased healthcare costs because of NVP, reduced well-being/quality of life, insufficient nutritional intake and inability to take iron supplements (256, 257). A translated Norwegian version of PUQE was recently validated (257).

5.2.3 Paper III The focus group study: Attitudes to and thoughts on treatment of NVP among pregnant women and general practitioners

This study applied a qualitative approach to assess attitudes to and experiences of treatment of NVP among women and general practitioners. The strength of this study was that focus group discussions were carried out with representatives of both the healthcare providers and patients. Although this study is not generalisable beyond the participants in this setting, the data provide valuable insight into thoughts and attitudes among GPs and pregnant women that may be useful for GPs and other healthcare personnel who are in contact with this patient group. It is acknowledged that being a novice researcher in qualitative research has its limitations. Focus group discussions were chosen as a method, since it is known to be well-suited to gaining insight into the participants' own experiences, thoughts and feelings (283). The group dynamic in a focus group may help people to explore and clarify their views, which also plays a vital role in uncovering new knowledge (230, 284, 285).

Sampling

Recruitment was slow in both groups of participants. This hindered a solely strategic sampling. The purpose of a strategic sampling is to identify specific groups of people who either possess characteristics or live in circumstances relevant to the social phenomenon in question, thereby enabling exploration from the widest possible range of views and/or experiences (234). With respect to the pregnant women, we had to apply snowball recruitment in order to enhance recruitment. This is obviously not ideal, as strategic sampling should be used to be able to widely explore the phenomenon in question. The Regional Committee for Ethics in Medical Research did not allow members of the research group to approach women for recruitment purposes. Instead, the recruitment process had to be conducted by healthcare personnel working at Kvinneklinikken, Haukeland University Hospital, who handed out an information pamphlet to women attending the clinic. Since the information pamphlet was sometimes handed out together with information about other studies, the recruitment process may have been impeded. However, despite the slow recruitment, our samples turned out to be quite diverse, with some exceptions. The women were generally highly educated, but age and parity varied among the participants. The low representation of women with lower levels of education may have affected our results. However, the women without a high education did not seem to feel constrained and they were well-accepted by the group, possibly because they had the illness in common.

GPs were recruited by contacting educational groups in the county of Hordaland suggested by the chair of the Committee for specialisation in general practice. Despite the slow recruitment, the GP sample was also relatively diverse, varying in age and gender. However, several GPs had less than five years' experience, which could partly explain the participating GPs' uncertainty about the choice of treatment after dietary and life style advice was given. Furthermore, the groups of GPs belonged to the same educational group, which may result in opposing points of view being withheld in order to avoid conflicts. However, based on a good dynamic in the groups during the sessions, and a seemingly high tolerance of contradictory

statements, this did not seem to constrain the discussions and the participants seemed comfortable with the setting.

Data collection, transcription and analysis

Semi-structured focus group discussions were conducted to collect the data. The focus group discussions were moderated by pharmacists/master's students in pharmacy. In the case of the focus group discussion with the pregnant women, a male master's student in pharmacy acted as moderator, which may have had an impact on the discussion. However, this was discussed prior to and after the discussion, and our impression was that this did not seem to hinder disclosure of relevant information about the phenomenon in question. It is possible that it may even have been an advantage in that the women might have provided even more detailed descriptions to enable the moderator, as a male, to comprehend the situations/experiences being shared. Being a pharmacist interviewing GPs, was also considered to have a possible impact on the results obtained. In order not to be perceived as 'intruders' who were there to criticise how the GPs practise their profession, this was stressed prior to conducting the discussions. Our impression was that the discussions resembled informal, natural conversations. This is probably due to a perceived natural setting in that healthcare professionals from one field shared experiences with healthcare professionals from another field. Open-ended questions were prepared in the interview guides, although they were sometimes deviated from in order to facilitate more detailed follow-up of responses or ideas of special interest.

The process of verbatim transcription of the audiotapes can also introduce errors (286). In an effort to reduce this risk, the audiotapes were transcribed by the moderator conducting the group discussion on the tape, with one exception. In the latter case, the moderator of the group quality-assured the transcript. Furthermore, the analyses of the transcripts were conducted by the researchers who had been present during the discussion, thereby enabling aspects of the interviews and group dynamics to be taken into account in the analytical process. There is nevertheless always the possibility of loss of information during translation, thereby affecting

reliability/dependability. The quotes presented in the paper were discussed with a native English speaker to try to reduce the risk of translational errors.

Systematic text condensation is a strategy that was developed to provide the novice researcher with a tool that facilitates a process of intersubjectivity, reflexivity and feasibility while maintaining a responsible level of methodological quality (255). It was therefore considered an appropriate strategy in our context.

Reliability and validity (dependability, credibility and transferability)

Though repeatability is often used as a measure of reliability and reproducibility in medical research, it is not a direct criterion for reliability or dependability in qualitative research (283). Data collection, analysis, interpretation and presentation are affected by the researcher's personality (283). Qualitative research acknowledges that there are several equally valid versions of knowledge (see section 1.9.2). Different researchers will interact with the group in different ways, follow different subthemes during the discussion, and find different nuances interesting when reading the same material etc. (283). While Mays and Pope recommend that the analysis should be repeated by more than one researcher to ensure validity/credibility (234), others argue that this is very difficult and perhaps not even appropriate due to the dynamic, socially constructed nature of reality (232). Armstrong et al. studied the extent to which six experienced qualitative researchers show consistency in their accounts after analysing a transcript and preparing an independent report (233). It was found that there was close agreement on the basic themes, but each analyst 'packaged' the themes differently (233). In this study, a group approach was applied in order to ensure the credibility of the transcripts, as well as when performing the analysis in order to improve dependability (234).

The potential for bias as a result of the preconceptions of the researcher has been identified as one possible problem with qualitative research. While Mays and Pope recommend that the theoretical framework and methods used in the research process should be accounted for (232, 234), others argue that the researchers' preconceptions

should be articulated, especially since a theoretical framework is not always applied (231, 232). The author's preconceptions are outlined in the foreword to this thesis.

The concept of validity, both in terms of credibility and transferability, should be carefully assessed in each step of the research process (230, 283). Mays and Pope describe different ways of improving validity in qualitative research (287). In this current study, the fact that the results from the focus group discussions with the two different groups of participants reflected each other to a great extent supports the validity and objectivity, or confirmability, of our findings. Respondent validation, 'member checking', may be used to promote validity (287). This was applied to the women, but not to the GPs. However, a limitation associated with respondent validation is that the interpretation produced by the researcher is designed for a wide audience and will be different from the interpretation or perception of an individual informant due to their different roles in the research process (287). Lastly, the importance of providing a clear exposition of the methods applied, by giving a clear description of the data collection and analyses (287), is acknowledged and endeavours have been made to provide one.

5.3 Discussion of results

5.3.1 Treatment of NVP

Though our findings indicate that nausea is prevalent, we found that the prevalence of treatment varied to a great extent between the countries. A low prevalence of NVP treatment (<20%) was found in several countries. Niebyl states that pharmacological treatment is necessary for approximately 10% of the women (42). However, no reference is provided with respect to what this estimate is based on. Gadsby et al. found that approximately 10% of women with NVP suffered from severe symptoms characterised by more than 300 hours of nausea and more than 40 episodes of vomiting in total (41, 48). As treatment of early symptoms is thought to reduce the risk of progression to more severe symptoms, as well as reducing the risk of hospitalisation (30, 32, 41), the proportion of women with NVP who are within the

target group for pharmacological treatment is probably higher than 10%. It is estimated that 35% of the women with NVP have symptoms that are of clinical significance (42), which is supported by the fact that 25% to 35% of the women with NVP had time lost from work due to NVP (48, 50). Furthermore, Vellacott et al. reported that daily vomiting occurred in 28% of the women with NVP (50).

The Norwegian study showed that a large proportion of the women with moderate to severe symptoms did not receive any pharmacological treatment. This finding indicates that Norwegian women are treated late in the course of their NVP. The newly revised guidelines in the NEL suggest that women with moderate NVP should be offered treatment (33), which may facilitate improvements in this regards.

In addition, we found a high degree of comorbidity among women with nausea. In particular, the association with symptoms of depression and with sick leave deserves attention, together with the finding of high prevalence of heartburn and reflux problems. Symptoms of depression and heartburn and reflux problems have also previously been associated with NVP (155), and treatment of heartburn and reflux problems has been found to alleviate NVP (208). Clinicians in contact with women with NVP should be aware of the high degree of comorbidity, and address these conditions if present.

NVP should be regarded as a significant public health issue, as it has been shown to result in negative physical, psychosocial and financial consequences (39, 52, 53, 82, 94, 96, 107, 108, 288). Optimal management is therefore of importance. It cannot be stressed enough that NVP is a condition that deserves and needs to be taken seriously by the medical community in order to reduce the suffering of these women to the greatest possible extent.

Treatment of NVP in a multinational perspective

In the multinational study, we found that approximately 7 out of 10 women in the total study population experienced nausea. This is in line with previous prevalence estimates in the literature (37). Though the prevalence of nausea was generally high

across all participating countries, some variations were found. To the best of our knowledge this is the first study to enable a reasonably direct comparison between several countries with respect to the prevalence of nausea during pregnancy, adding to the literature on the subject. However, we did not have data on the severity of symptoms. Fewest women reported nausea in Russia, Croatia and Serbia, while most women reported nausea in Iceland, Sweden and the USA. The comprehensive review conducted by Einarson et al. in 2013 also found a wide range of prevalence estimates reported from various countries (37). However, as the studies differed in the methodologies applied, such as varying definitions of NVP, inclusion criteria and source population, direct comparison was problematic. Einarson et al. state that little is known about the prevalence of NVP in the Eastern European countries and less developed countries in general. The observed dissimilarities between countries may be explained by cultural differences that are reflected in differences in self-perceived illness, differences between various ethnic groups' genetic predisposition, or differences in healthcare systems. Our study adds to the literature by providing prevalence rates for the participating countries in Eastern Europe, but little is known about the countries in South America, Africa and large parts of Asia (37).

Overall, of the respondents who had experienced nausea, 27% had used some type of treatment against nausea, and 18% had used conventional medicines to treat this complaint. Previously reported prevalence estimates for use of conventional medicines for nausea are shown in table 3, section 1.8 (52-54, 94, 166, 197, 218-221, 224). However, direct comparison with previously reported prevalence estimates is problematic due to large variations in the methodologies applied and differences between the countries in which the research was conducted. Furthermore, as we do not have data on the severity of nausea, we cannot determine whether the respondents suffered from mild symptoms that were sufficiently managed by non-pharmacological treatments, such as changes in diet and lifestyle that may explain our result.

Nevertheless, our observed country-specific estimates of use of treatment showed large variations. Women with nausea residing in Slovenia, Croatia, Finland and

Poland showed the lowest use of medicines for nausea, as opposed to women from Canada, France, Sweden and Switzerland, who showed the highest use. Several of our findings can be explained by cultural differences and differences in access to prenatal care and treatments, as well as their relative costs. Differences between various national guidelines or lack thereof may also be a reason. Furthermore, variations in the women's self-perception of severity of symptoms and the general practitioners' and women's risk perception as regards the use of medicines during pregnancy are reflected in both groups' attitude to treatment, and this may also explain our findings (289-292). According to the current literature, the extent of use of medicines against nausea has been highest in Canada, Australia and France (see Table 3 in section 1.8), which correlates well with our results.

No data were found about the treatment of nausea in countries in Eastern Europe. However, Serbia is known to have a low extent of use of medicines in general during pregnancy (15, 293). Interestingly, compared to the prevalence of HG of 1.1% found in a recent meta-analysis (37), a relatively high prevalence of 3% of HG is reported in Russia (294), and a high prevalence of 10% (17.5% of 58% with nausea) of severe NVP is reported in Serbia (295). Since treatment of early symptoms is believed to reduce the risk of progression to more severe symptoms as well as hospitalisation (30, 32), it may be hypothesised that the high prevalence of HG/severe symptoms could be explained by suboptimal treatment, based on the low estimates of use of medicines detected in these countries. In most Eastern European countries, antacids were the most commonly used conventional medicines against nausea, which deviates from the first line treatment recommendations for NVP in major guidelines (27, 28, 30-32). This could indicate that comorbidities associated with nausea are treated more than the nausea itself.

In the vast majority of countries, antihistamines and metoclopramide were the most commonly used conventional medicines against nausea. In the USA, ondansetron was most commonly used. The differences found between countries with respect to the types of treatments most commonly used are in line with findings from a study of HG treatments (226). This study found that antihistamines were most commonly used in

Canada and that serotonin inhibitors were most commonly used in the USA, whereas Australia had the highest reported use of promotility agents such as metoclopramide (226). The same study also noted that women from Canada used less intravenous hydration and parenteral nutrition than women from the USA, commenting that this could be explained by more efficient treatment by physicians made possible by the availability of Diclectin® on the Canadian market (226). This is in line with another study finding, namely that Canadian women had less lost time from paid work, were hospitalized less often due to NVP and had suffered less weight loss when compared to American women (224).

The high use of antihistamines is in accordance with recommendations in major guidelines (27, 28, 30-32). Dopamine antagonists such as metoclopramide are commonly referred to as second line treatment options, after doxylamine/pyridoxine or other antihistamines (27, 30-32). While no increased risk of malformations is associated with the use of either antihistamines or metoclopramide (164, 175, 176), both the foetal and maternal safety of ondansetron has recently been questioned (193). Concerns about cardiac malformations have been raised. Though two Danish studies reporting opposing results regarding the risk of cardiac malformations made it difficult to conclude (194, 195), the concerns were recently strengthened when a third study also detected a modestly increased risk of cardiovascular and cardiac septum defects (196). As regards maternal safety, cardiovascular safety concerns were raised by the FDA in 2011, suggesting that ondansetron could cause QT prolongation, leading to Torsade de Pointes (200). Lately, maternal safety concerns have also been raised with respect to metoclopramide. EMA's recommendation of restricting the use of metoclopramide to maximum five days will probably limit metoclopramide's role in the treatment of this pregnancy complaint (189). The consequence is that pregnant women are left with fewer available agents for the treatment of NVP. The safety documentation pertaining to the use of the other dopamine antagonists, such as chlorpromazine and prochlorperazine, during pregnancy is less extensive, although the available evidence generally points to both agents being safe to use during pregnancy (9, 182-184, 187). Benefit-risk assessments may in some cases still favour

treatment by metoclopramide, and pregnant women prescribed metoclopramide for NVP should be closely followed up with respect to neurologic side effects.

Treatment with herbal medicine among women with nausea was highest in Australia, Iceland and Slovenia; and lowest in Sweden, Croatia and Finland. The high use in Australia and the low use in Sweden are in line with previous findings (123, 296, 297). Pregnant Australian women have also previously been found to use herbal drugs, and CAM in general, to a high extent (123, 296). At the opposite end of the scale, a previous study based on the Swedish Medical Birth Register reported a prevalence rate as low as 0.9% for the use of herbal drugs among pregnant women of whom surprisingly few, only 0.6% of the users, had used ginger (297). The low use of ginger was mainly explained by high use of OTC antihistamines against NVP (297), an explanation that could probably be extrapolated to apply to our result as well. In 2009, the Finnish food safety agency, Evira, issued a warning based on the precautionary principle about the use of ginger during pregnancy due to alleged harmful constituents posing a risk to the foetus (298). That may explain the low use in this particular country.

Ginger was the most commonly ingested herbal agent for NVP. This was not surprising since ginger is included in major guidelines for the treatment of NVP (27, 28, 30-32).

Treatment of NVP in Norway

Compared to the multinational study, we found a relatively high prevalence of 38.9% for the use of medicines for NVP in the Norwegian study. This is probably due to the fact that the women who participated in the latter study generally suffered from moderate or severe symptoms, 61.7% and 29.5%, respectively. Not surprisingly, medicines were increasingly used with increasing severity of NVP. Among women with mild NVP, only 8.2% had used any antiemetics. Note, however, that negative impact on the women's quality of life and a clinically important prevalence of psychosocial problems have also been found among women with mild NVP (53, 95). Although the effects is more magnified in moderate or severe NVP, significant

adverse effects on eating and nutrition, domestic and occupational and social life were also detected among women with mild NVP in an American study (95). In a Canadian study, one in five women with mild NVP reported feelings of depression always or most of the time, and 43% reported adverse effects on their partner's daily life (53). We also found that a large proportion of the women with moderate and severe NVP, 70.2% and 32.9%, respectively, did not use any antiemetics, which warrants attention. Optimal management is particularly important in cases of severe NVP/HG, since it was found that use of antiemetics was more frequent among women who only considered and women who never considered termination compared to women who did terminate their pregnancy due to NVP/HG (97). Moreover, almost two-thirds of the women had been on sick leave due to NVP, many of whom did not receive antiemetics prior to being put on sick leave or at any time during their pregnancy. These findings could either be due to healthcare personnel being reluctant to prescribe any antiemetics or to the women not being willing to take medicines.

Meclizine was the most commonly used medicine for NVP, and metoclopramide came second, which is in accordance with the Norwegian guidelines (33, 34). However, approximately half of the women using only one medicine had not used an antihistamine, indicating that deviations from the treatment guidelines occur. The choice of treatment is based on an individual risk-benefit assessment together with clinical judgement, which may explain this finding. The fact that metoclopramide had almost as many users as meclizine was surprising, especially in light of the recent warning issued by the EMA. Sub-analyses including women who were pregnant at the time of participation revealed that a large proportion of the women using metoclopramide used it for more than one week. These women must have used metoclopramide after the EMA warning was issued, indicating that the EMA warning is not generally known or accepted among GPs. The high degree of use of metoclopramide can probably be explained the fact that the majority of the respondents were suffering from moderate and severe symptoms, which may not have been sufficiently managed by antihistamines. Ondansetron was the third most commonly used medicine, used by 7% of the women. While treatment with either

meclizine or metoclopramide was initiated by a general practitioner, ondansetron was most often initiated by a gynaecologist or a hospital physician. It is listed as a third line treatment option recommended for patients with more severe symptoms in several guidelines (27, 31, 34). This is in line with our finding that women with severe NVP or who were hospitalised were significantly more likely to have used ondansetron.

Nearly all the women reported having tried dietary and lifestyle changes in an effort to reduce the NVP symptoms. The use of CAM was high, which is in line with findings from several prior studies (14, 17, 124, 223, 299). As in the multinational study, ginger was the most commonly used herbal medicine. Acupressure was also a commonly used CAM. CAM use as a whole was greater than use of conventional medicines, but herbal medicines alone were used to an almost equal extent as conventional medicines. Although herbal medicines were used by only half as many women as conventional medicines overall in the multinational study, among the Norwegian women in that study, the use of herbals was almost equal to the use of conventional medicines, which largely concurs with our results in this study. The extensive use of CAM and changes in dietary and lifestyle are in line with guidelines recommending first trying conservative approaches (such as dietary and lifestyle changes, ginger, acupressure and/or acupuncture) before using any medicines.

5.3.2 Factors associated with the use of treatment against nausea

In the multinational study, it was found that respondents who had lower education, worked as healthcare professionals or women with a multiple pregnancy were more likely to use medicines against nausea. The Norwegian study also identified education and employment status as factors predicting use. However, in this study it was found that fewer women with a master's degree, or who were unemployed used medicines for NVP compared to women who had a bachelor's degree or were currently employed. Though our findings in the two studies were not identical, they are not necessarily contradictory. Direct comparison is problematic due to differences in variable classification.

Education and employment status are both factors that have also previously have been associated with the use of medicines for NVP. A previous study from Sweden found that women with lower levels of education used medicines to a greater extent than women with higher education (166), and Markl et al. from Germany found that unemployed women and women on welfare had a higher chance of getting a prescription for medicines for NVP than 'blue and white collar workers' (219). The observed discrepancies may be explained by cultural differences between the study populations.

The association between the use of medicines and multiple pregnancy could indicate that the use of medicines may act as a marker of severe forms of nausea, as it has previously been found that multiple pregnancy increases the risk of nausea (300). The severity of nausea was indeed strongly associated with the use of treatment in the Norwegian study, which is in line with previous studies (53, 79). Since no firm conclusion can be drawn with respect to maternal characteristics predicting use of treatment, exploring women's beliefs and the severity and impact of symptoms is probably a better approach.

5.3.3 Safety of use of ginger during pregnancy

Ginger was frequently used for NVP in both the multinational and the Norwegian study. However, little is known about the safety of ginger, other than that no reports of increased risk of malformations or any other impact on pregnancy outcomes have been filed, neither from a rather small prospective study including 187 pregnant women who used ginger, nor any of the randomised controlled clinical trials studying the effect of ginger against NVP (143, 154). Furthermore, no case reports about any negative impact of ginger use on pregnancy outcomes have been detected.

To our knowledge, this study is the largest study yet to investigate the safety of ginger use in pregnancy, and the results are reassuring: using ginger during pregnancy does not seem to increase the risk of malformations or negative pregnancy outcomes such as still birth/perinatal death, preterm birth, low birth weight and low Apgar score. A small increased risk of vaginal bleeding was observed among ginger

users. However, when the analyses were restricted to more severe bleeding, no association was found. Moreover, sub-analyses stratified by timing of use did not detect any association between the bleeding outcomes and use of ginger either.

The results of this study add valuable knowledge that strengthens our confidence in the findings of the safety evaluation study by Portnoi et al. and the clinical trials (154). Since ginger was commonly used both in Norway and internationally, these findings have valuable clinical implications as they provide healthcare professionals with more evidence when discussing ginger use with pregnant patients. However, women struggling with severe symptoms and/or heartburn and reflux problems should probably be recommended to avoid ginger, as ginger may exacerbate these symptoms (156).

In Norway, herbal products are available as herbal medicinal products classified according to well-established or traditional use as described in the EU regulations (301), and as dietary supplements (302). For a product to be registered as a herbal medicinal product, specific requirements apply with respect to the demonstration of traditional use within the EU, the safety and quality of the product, including complying with good manufacturing practice (GMP) and European Pharmacopeia standards (262), as well as compulsory pharmacovigilance. In contrast, dietary supplements are only notified to the Norwegian Food Safety Authority, and pharmacovigilance of these products is not compulsory. To date, only 14 herbal medicinal products exist on the Norwegian market (303), none of which contain ginger, which means that most herbal medicines are unregulated products classified as dietary supplements. Consequently, little is known about their quality, safety and effectiveness of use. This should be taken into consideration when herbal products are considered for use by pregnant women.

5.3.4 Attitudes to and thoughts about treatment of NVP

The qualitative study conducted with GPs and pregnant women provided a deeper insight into both groups' attitudes to and thoughts on treatment of NVP that adds to the findings from the multinational and the Norwegian study of treatment of NVP.

Both studies indicate the presence of suboptimal treatment of NVP, which is especially important among women with moderate and severe symptoms.

The most important finding in the focus groups study is that the pregnant women and the GPs seem to talk at cross purposes. While the women wanted their problems to be acknowledged, the GPs emphasised normalising the symptoms. This was done with good intentions in an effort to reduce the women's possible anxiety about nausea harming their foetus. Although it is probably worth mentioning, too much emphasis on normalisation or trivialisation of symptoms can make the women feel that they are not being taken seriously. A low level of belief in the patients may result in delayed intervention, and consequently affect the time required for recovery (215). This illustrates the importance of a good patient-GP relationship. However, a recent master's project that collected data on various aspects of the experience of HG among Norwegian women found that half of the women had not initially been taken seriously by their GP, and 21% of the women changed their GP due to inadequate treatment (304). With the exception of hospital physicians, the women had the impression that there was a lack of knowledge about HG among healthcare personnel. Both of these findings are in line with our findings, and may contribute to a delay in the initiation of treatment in primary care. Healthcare personnel should also inform women that symptoms may worsen to become as severe as merits hospitalisation. Hence, they should advice women on when to seek medical care, and explain the benefit and importance of seeking help to reduce symptom severity.

Furthermore, the women missed being properly evaluated in an effort to address symptom severity and impact. This was more or less confirmed by the GPs, who admitted that, due to a busy schedule, at the first antenatal consultation, and due to the fact that the presence of nausea was expected, nausea was simply confirmed without being carefully assessed. The fact that national and international guidelines stress the importance of reassuring women that nausea is a normal part of pregnancy may explain these findings (28, 35, 36). The lack of proper evaluation has been documented in previous studies as well. An American study from 2013 reported that two thirds of the women with NVP missed being evaluated by professionals about the

impact of their symptoms on daily life functioning (95). However, obtaining information about severity and impact of symptoms may facilitate healthcare personnel in providing individualised treatment strategies.

Sick leave was a topic that was spontaneously brought up by the GPs when treatment of NVP was addressed. The impression was that sick leave was a measure commonly used by the GPs as part of the treatment of NVP, often without concomitant prescribing of medicines, which is in line with previous findings in the Norwegian study of treatment of NVP. Sick leave was also associated with nausea in the multinational study. A prior study from Norway found that NVP was one of the most common reasons for sick leave during pregnancy, being responsible for 33% of all sick leave during pregnancy (3). Most of the women in the focus group had been on sick leave due to NVP. However, the women emphasised that, if it was possible to keep a part-time position, this was welcomed as it enabled some social contact. Feelings of isolation have previously been reported by women suffering from NVP (96). Though sick leave enables women to rest when necessary during daytime, it does not provide relief from the symptoms when caring for other children or doing household chores and should consequently not be viewed as an adequate substitute for antiemetics. Furthermore, prescribing sick leave without the concomitant prescription of antiemetics may send a message to the women that there is nothing more to be done, leaving the women isolated in their own misery. Sick leave could also have been perceived as an 'easy way out' of the treatment dilemma for both parties, as it is a 'treatment' option that does not involve exposing the foetus to drugs, which both groups, the women and the GPs, view as potential teratogenic substances.

The GPs also seemed confident about giving dietary and lifestyle advice to the women. The advice referred to by the GPs included dry biscuits, eating before getting up in the morning and ensuring an adequate intake of fluid. However, detailed dietary and lifestyle changes that help to maintain adequate hydration and nutritional status are available (121), which could also be beneficial for Norwegian women to know about.

Both groups showed reluctance about treating NVP with medicines. References to the thalidomide tragedy were made by both groups. The thalidomide tragedy taught us an important lesson that medicines may impact foetal development. The take-home message from this tragedy should rather be a lesson about *how* to use medicines, not to strive for complete *avoidance*. Even though the women in the focus group discussions clearly wanted their problems to be acknowledged, they sent rather mixed messages about treatment. They criticised the GPs for not offering any prescription of medicines, but they clearly tried to avoid using medicines.

This is in line with the findings revealed in the Norwegian cross-sectional study that women's beliefs had an important impact on their use of medicines for NVP. Severity of symptoms was also associated with the women's attitudes. Our findings may indicate that the women become more open to treatment the larger the burden of the illness, which is reasonable. Still, even women with severe symptoms generally showed a restrictive attitude towards medicines. These findings show that there is a need for comprehensive and reassuring information about treatment options to reduce women's anxiety and insecurity, which influence their willingness to adhere to treatment (305). It has been shown that counselling and proper risk communication can reduce women's negative beliefs about medicines and increase adherence during pregnancy (306, 307). Taking time to explore women's perceptions and knowledge could be essential to ensure adequate NVP treatment and should be incorporated in clinical guidelines.

However, the GPs that participated in the focus group discussions seemed to be uncertain about medical treatment of NVP, and they wanted a medicine with NVP as approved indication, especially in light of the warning about metoclopramide issued by the EMA. They also expressed a lack of belief in the effect of commonly used medicines against NVP. So, before GPs can counsel the women and provide proper risk communication about treatment of NVP, they must first have accurate knowledge about and confidence in safe treatment options for this complaint.

5.4 Clinical implications and future perspectives

Several of the findings in this thesis are of clinical importance in the fields of obstetrics, primary care and pharmacy. The prevalence rate of treatment of NVP showed intercountry variations, and the type of treatment of NVP most commonly used also varied across countries. As discussed above, there may be several explanations for the detected variations, including differences between national guidelines or lack thereof. Efforts should be made to educate healthcare personnel involved in pregnancy care about the available evidence-based information concerning treatments for NVP. Relevant sources of evidence-based information should be easily accessible and made well-known to the medical community. Guidelines should be updated in accordance with the findings from rigorous and repeated studies. They should be clearly written, so that they are easily comprehensible, and they should offer conclusive guidance to avoid leaving the clinicians in a dilemma about whether to medicate or not, which may give rise to differences in the type of care offered to the patients. An important step forward in Norway is the recently adopted revision of the NVP/HG guidelines in the NEL, in which PUQE is now included and impaired quality of life among women with NVP/HG is more directly addressed (33).

The prevalence of nausea also varied to some extent between countries. This is the first study to enable a reasonably direct comparison to be made between countries with respect to the prevalence of nausea, adding to the literature on the subject. However, we did not have data on the severity of symptoms. Our study adds to the literature by providing prevalence rates for the participating countries in Eastern Europe, but little is still known about the countries in South America, Africa and large parts of Asia (37). Future studies should aim to close this knowledge gap.

The prevalence rate for use of medicines in Norway was low compared to many other countries, and, according to our findings from the study conducted among Norwegian women, many women with moderate and severe NVP did not use any medicines. Furthermore, the qualitative study indicated that both GPs and pregnant women were

wary of prescribing or taking antiemetics for NVP. GPs seemed to be little aware of the negative consequences of NVP, and a proper clinical examination of the severity of the symptoms was seldom performed due to lack of time. These findings deserve attention. As elaborated above, women with NVP have an impaired quality of life and a high burden of comorbidity. The consequences of not being properly treated can be devastating (38, 39, 41, 84, 96, 97, 104, 106) and need to be acknowledged by healthcare providers involved in pregnancy care, so that women presenting with NVP are taken seriously. The newly revised NEL guidelines recommend that women who are classified as having moderate NVP according to PUQE should be offered pharmacological treatment (33). However, it is important to also assess the impact of symptoms on daily life functioning, mental health and occupational life, and to evaluate the woman's social support system. Moreover, clinicians should pay attention to the high degree of comorbidity among women with NVP and examine these women for symptoms of depression, and heartburn and reflux problems, which should be addressed if present. Future studies should investigate whether treatment of early symptoms reduces sick leave and progression to severe symptoms, as well as investigating whether combination therapy should be preferred over monotherapy, and whether daily and consistent dosing is superior to an 'as needed' regime. The treatment offered in primary care should also be investigated in more detail, and the factors that influence the decisional process with respect to medical treatment for NVP should be studied.

Advice on dietary and lifestyle changes seems to be a welcome option among women. The women would probably benefit from more detailed advice about dietary and lifestyle changes that contribute to maintaining adequate hydration and nutritional status (121). This knowledge should be obtained by Norwegian healthcare providers and disseminated to the pregnant population.

Since ginger was shown to be widely used for NVP, our findings about the safety of using ginger during pregnancy were reassuring and may help healthcare personnel when discussing use of ginger during pregnancy. However, they need to be replicated by future studies in order to draw a firm conclusion.

Our findings about women's beliefs and attitudes are also of interest. Awareness of the association between women's beliefs and use could assist clinicians when discussing treatment with pregnant women. Our findings indicate that women probably need comprehensive and reassuring information before considering using any medicines. But before GPs can take this position, they must obtain updated evidence-based knowledge and have confidence in the treatments available for NVP. The GPs in the focus group discussion wanted a medicine with NVP as approved indication, which should be noted by the health authorities in Norway.

This is also a context in which pharmacists can prove valuable. Pharmacists are easily accessible healthcare personnel for pregnant women who need advice about how to handle symptoms of NVP. Pharmacists have a unique opportunity to counsel women early in their pregnancy about recommended dietary and lifestyle changes to relieve symptoms of NVP and facilitate adequate hydration and nutritional status. Though no medicine is available OTC in Norway for NVP, pharmacists can play an important role in educating women that there are medicines available on prescription that can help, and in providing proper risk communication and encouraging optimal management of NVP. It is therefore important that pharmacists are trained in how to counsel these women, so that they can give specific advice on how to best manage NVP in practice. Pharmacists could also play an important role in detecting women who need close follow-up and adequate medical treatment, and refer them to their GP when appropriate.

So far, very little research has been conducted on maternal safety of use of metoclopramide for NVP. The few available randomised control trials and other studies primarily evaluate the effectiveness of metoclopramide for NVP (174, 177-179). Larger studies specifically addressing maternal safety are warranted.

Because of the EMA warning about metoclopramide (189), other dopamine-antagonists may be increasingly used. More evidence is needed of the safety, both maternal and foetal, of the use of chlorpromazine and prochlorperazine. There is also

conflicting evidence about the safety of ondansetron intake during pregnancy, and further studies are needed before a firm conclusion can be drawn.

In conclusion, our findings indicate that improvements should be made with respect to the health care provided for pregnant women suffering from NVP. We appear to be still struggling with the aftermath of the thalidomide tragedy that taught us an important lesson about how medicines can impact foetal development. Both GPs and women have the thalidomide story and/or the fear of drug teratogenicity at the back of their mind, which probably affects their decision-making as regards treatment. This is a paradox, however, since safe treatment options exist for NVP today. Acknowledging that NVP is a significant public health issue, optimal management of NVP will provide women, the healthcare system and the society as a whole, with great relief.

Advice to healthcare professionals

- As stated by participants in the Norwegian cross-sectional study of treatment of NVP.

'*Please take us seriously! Listen to us! We are not all just hysterical, hormonal mothers-to-be.*' A 22-year-old new mother from Western Norway.

'*Take NVP seriously. Despite knowing that it will pass, for many women, it means several months of incapacitation. It is important to be knowledgeable about treatment and medicines. Don't trivialise the condition. Don't say things like: you should be glad that you are able to have children.*' A 26-year-old new mother from South East Norway.

'*Take pregnant woman seriously. It is a high threshold to cross to come and ask for help. It is therefore very important that we are met with understanding.*' A 40-year-old woman from Western Norway in pregnancy week 31.

'*Listen to each and every one of us, and tell us that something can be done. At the same time, remind us that these problems will only last for a short period of our lives.*' A 23-year-old woman from Western Norway in pregnancy week 34.

'*Take us seriously. Treat us earlier when necessary. Give concrete advice! Don't just say: this is normal.*' A 31-year-old woman from South East Norway in pregnancy week 18.

'*It is important to be supportive, and show that you understand that NVP can be tough, even in the absence of vomiting. Offer to help, explain about the risks and benefits of medicines.*' A 28-year-old woman from Western Norway in pregnancy week 28.

References

1.	Jahren A, Erikssen HØ. Danske debattanter: -Gravide blir sykemeldte for lett (in Norwegian). English: Danish debaters: -Pregnant women go on sick leave too easily. Verdens Gang (VG). 2014 (Accessed 20 December 2015). Available from: http://www.vg.no/nyheter/innenriks/helse/danske-debattanter-gravide-blir-sykmeldte-for-lett/a/10128912/.
2.	Kaluza S. Sykemeldte gravide: Noen ganger har jeg lyst til å spytte i ansiktet på folk som sier "svangerskap er ingen sykdom" (in Norwegian). English: Pregnant women on sick leave: Sometimes I want to spit in the face of people saying "pregnancy is not a disease". klikk.no. 2014 (Accessed 20 December 2015). Available from: http://www.klikk.no/foreldre/article889423.ece.
3.	Dorheim S, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. BJOG. 2013;5:521-30.
4.	The Norwegian Welfare and Labour Administration. (2011) Sickness benefits for employees. The Norwegian Welfare and Labour Administration. (Accessed 19 August 2015). https://www.nav.no/en/Home/Benefits+and+services/Relatert+informasjon/Sickness+benefits+for+employees.283831.cms.
5.	Miller MT, Strömland K. Teratogen update: thalidomide: a review, with a focus on ocular findings and new potential uses. Teratology. 1999;60(5):306-21.
6.	Thalidomide - Victims Association of Canada. Thalidomide - The Canadian Tragedy. (Accessed 30 November 2015). http://www.thalidomide.ca/the-canadian-tragedy/.
7.	McBride WG. Thalidomide and congenital abnormalities. The Lancet. 1961;278(7216):1358.
8.	Lenz W, Pfeiffer RA, Kosenow W, Hayman D. Thalidomide and congenital abnormalities. The Lancet. 1962;279(7219):45-6.
9.	Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 8th ed. Philadelphia: Lippinncott Williams & Wilkins; 2008.
10.	Diav-Citrin O, Koren G. Human teratogens: A critical evaluation. Motherisk; 2002.
11.	Fisk NM, Atun R. Market failure and the poverty of new drugs in maternal health. PLoS medicine. 2008;5(1):e22.
12.	Neutel CI, Johansen HL. Measuring drug effectiveness by default: the case of Bendectin. Canadian journal of public health = Revue canadienne de sante publique. 1995;86(1):66-70.
13.	Niebyl JR, Briggs GG. The pharmacologic management of nausea and vomiting of pregnancy. The Journal of family practice. 2014;63(2 Suppl):S31-7.
14.	Adams J, Lui CW, Sibbritt D, Broom A, Wardle J, Homer C, et al. Women's use of complementary and alternative medicine during pregnancy: a critical review of the literature. Birth. 2009;36(3):237-45.
15.	Lupattelli A, Spigset O, Twigg M, Zagorodnikova K, Mårdby A, Moretti M, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ open. 2014;4(2):e004365.
16.	Kennedy DA, Lupattelli A, Koren G, Nordeng H. Herbal medicine use in pregnancy: results of a multinational study. BMC Complement Altern Med. 2013;13:355.
17.	Nordeng H, Bayne K, Havnen GC, Paulsen BS. Use of herbal drugs during pregnancy among 600 Norwegian women in relation to concurrent use of conventional drugs and pregnancy outcome. Complement Ther Clin Pract. 2011;17(3):147-51.
18.	Daw JR, Hanley GE, Greyson DL, Morgan SG. Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf. 2011;20(9):895-902.
19.	Schaefer C, Peters P, Miller R, editors. Drugs During Pregnancy and Lactation. London: Elsevier; 2007.
20.	Mattison D. Clinical pharmacology during pregnancy: Academic Press; 2013.
21.	Fairweather DV. Nausea and vomiting in pregnancy. Am J Obstet Gynecol. 1968;102(1):135-75.

22.   Schjøtt-Rivers E. Hyperemesis Gravidarum: Clinical and Biochemical Investigations. Acta Obstetricia et Gynecologica Scandinavica. 1938;18(S1):1-248.
23.   Kemp W. Hyperemesis gravidarum treated as a temporary adrenal cortex insufficiency. Canadian Medical Association Journal. 1933;28(4):389.
24.   Buckwalter JG, Simpson SW. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. Am J Obstet Gynecol. 2002;186(5):S210-S4.
25.   FitzGerald CM. Nausea and vomiting in pregnancy. British journal of medical psychology. 1984;57(2):159-65.
26.   Atlee H. The treatment of the pernicious vomiting of pregnancy. Canadian Medical Association Journal. 1925;15(4):388.
27.   Quinlan J. Nausea and vomiting in pregnancy: BMJ Best Practice; 2015. Available from: http://bestpractice.bmj.com/best-practice/monograph/999.html.
28.   National Collaborating Centre for Women's and Children's Health. Commissioned by National Institute for Health and Clinical Excellence. 6.1 Nausea and vomiting in early pregnancy. Antenatal care: routine care for the healthy pregnant woman. 2 nd ed. London: RCOG Press; 2008.
29.   Maltepe C, Koren G. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum--a 2013 update. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(2):e184-92.
30.   Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24(10):817-31; quiz 32-3.
31.   Smith J, Refuerzo J, Ramin S. Treatment and outcome of nausea and vomiting of pregnancy. UpToDate. 2014.
32.   ACOG (American College of Obstetrics and Gynecology) Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12-24.
33.   Norsk Elektronisk Legehåndbok. (2015) Norsk Elektronisk Legehåndbok (in Norwegian). English: Norwegian Electronic Medical Handbook. Norsk Helseinformatikk. (Accessed 07 December 2015). http://legehandboka.no/.
34.   The Norwegian Society of Obstetrics and Gynecology. (2014) Veileder i fødselshjelp (in Norwegian). English: Obstetric guidelines issued by The Norwegian Society of Obstetrics and Gynaecology (NGF). http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/Emesis-og-hyperemesis-gravidarum/. English version available at:
http://www.nfog.org/files/guidelines/7%20NGF%20Obst%20hyperemisis%20Vikanes.pdf.
35.   Norsk Legemiddelhåndbok (in Norwegian). English: Norwegian Medicines Handbook [Internet]. 2015 (Accessed 09 April 2015). Available from: http://legemiddelhandboka.no/Terapi/søker/+%2Bsvangerskapskvalme/19493.
36.   The Norwegian Directorate of Health and Social Affairs. Nasjonale faglige retningslinjer: Retningslinjer for svangerskapsomsorgen (in Norwegian). English: A National Clinical Guideline for antenatal care. 2005 ed: Sosial og helsedirektoratet (in Norwegian). English: The Norwegian Directorate of Health and Social Affairs; 2005.
37.   Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(2):e171-83.
38.   Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. Contraception. 2007;76(6):451-5.
39.   Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM. The psychosocial burden of hyperemesis gravidarum. Journal of perinatology : official journal of the California Perinatal Association. 2008;28(3):176-81.

40.   Ismail SK, Kenny L. Review on hyperemesis gravidarum. Best Pract Res Clin Gastroenterol. 2007;21(5):755-69.

41.   Gadsby R, Barnie-Adshead AM. Nausea and vomiting of pregnancy: Clinical information about nausea and vomiting of pregnancy, its relation to various aspects of women's personal and obstetric histories and other significant factors related to nausea and vomiting of pregnancy or hyperemesis gravidarum: a literature review. (Accessed 07 October 2015). https://www.google.no/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CBwQFjAAah UKEwii9LmJhrHIAhWkfHIKHVXpCG0&url=https%3A%2F%2Fwww.pregnancysicknesssupport.org.uk %2Fdocuments%2FNVP-lit- review.pdf&usg=AFQjCNHMaEQTBNvyoGfQAUCleTfV1BFRMw&sig2=yeBGOusQFnZ-z6C3EMVjFQ.

42.   Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. The New England journal of medicine. 2010;363(16):1544-50.

43.   World Health Organization. (2015) International Statistical Classification of Diseases and Related Health Problems 10th Revision. (Accessed 05 November 2015). http://apps.who.int/classifications/icd10/.

44.   Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. J Obstet Gynaecol Can. 2009;31(9):803-7.

45.   Maltepe C. Surviving morning sickness successfully: from patient's perception to rational management. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2014;21(3):e555-64.

46.   Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. Edinburgh: Churchill Livingstone; 2003.

47.   Neal MJ. Medical Pharmacology at a Glance. 5th edition ed. Oxford: Blackwell Publishing; 2005.

48.   Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43(371):245-8.

49.   Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182(4):931-7.

50.   Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. Int J Gynaecol Obstet. 1988;27(1):57-62.

51.   Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol. 1985;66(5):612-6.

52.   Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol. 2000;40(4):397-401.

53.   Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol. 2000;21(3):129-36.

54.   Chandra K, Magee L, Einarson A, Koren G. Nausea and vomiting in pregnancy: results of a survey that identified interventions used by women to alleviate their symptoms. J Psychosom Obstet Gynaecol. 2003;24(2):71-5.

55.   Zhou Q, O'brien B, Relyea J. Severity of nausea and vomiting during pregnancy: what does it predict? Birth. 1999;26(2):108-14.

56.   Swallow BL, Lindow S, Masson E, Hay D. Development of an instrument to measure nausea and vomiting in pregnancy. Journal of Obstetrics & Gynecology. 2002;22(5):481-5.

57.   Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S220-7.

58.   Power Z, Campbell M, Kilcoyne P, Kitchener H, Waterman H. The Hyperemesis Impact of Symptoms Questionnaire: development and validation of a clinical tool. Int J Nurs Stud. 2010;47(1):67-77.

59.   Chin R, Lao T. Low birth weight and hyperemesis gravidarum. Eur J Obstet Gyn R B. 1988;28(3):179-83.

60.   Chin RK. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. Eur J Obstet Gyn R B. 1989;33(3):215-9.

61.   Weigel MM, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. American journal of epidemiology. 1988;127(3):562-70.

62.   Godsey RK, Newman RB. Hyperemesis gravidarum. A comparison of single and multiple admissions. The Journal of reproductive medicine. 1991;36(4):287-90.

63.   Verberg M, Gillott D, Al-Fardan N, Grudzinskas J. Hyperemesis gravidarum, a literature review. Human Reproduction Update. 2005;11(5):527-39.

64.   Bogen JT. Neurosis: a Ms-diagnosis. Perspectives in biology and medicine. 1994;37(2):263-74.

65.   Goodwin TM. Nausea and vomiting of pregnancy: an obstetric syndrome. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S184-9.

66.   Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. BMJ. 2011;342:d3606.

67.   Sherman PW, Flaxman SM. Nausea and vomiting of pregnancy in an evolutionary perspective. Am J Obstet Gynecol. 2002;186(5):S190-S7.

68.   Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol. 2008;141(1):13-7.

69.   Vikanes A, Skjaerven R, Grjibovski AM, Gunnes N, Vangen S, Magnus P. Recurrence of hyperemesis gravidarum across generations: population based cohort study. BMJ. 2010;340:c2050.

70.   Corey LA, Berg K, Solaas MH, Nance WE. The epidemiology of pregnancy complications and outcome in a Norwegian twin population. Obstet Gynecol. 1992;80(6):989-94.

71.   Clark SM, Costantine MM, Hankins GD. Review of NVP and HG and Early Pharmacotherapeutic Intervention. Obstet Gynecol Int. 2012;2012:252676.

72.   Lee NM, Saha S. Nausea and vomiting of pregnancy. Gastroenterology clinics of North America. 2011;40(2):309-34.

73.   Rodien P, Jordan N, Lefevre A, Royer J, Vasseur C, Savagner F, et al. Abnormal stimulation of the thyrotrophin receptor during gestation. Hum Reprod Update. 2004;10(2):95-105.

74.   Koch KL. Gastrointestinal factors in nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5):S198-S203.

75.   Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(3):695-703.

76.   Niemeijer MN, Grooten IJ, Vos N, Bais JM, van der Post JA, Mol BW, et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;211(2):150. e1-. e15.

77.   Munch S. Chicken or the egg? The biological–psychological controversy surrounding hyperemesis gravidarum. Social Science & Medicine. 2002;55(7):1267-78.

78.   Simpson SW, Goodwin TM, Robins SB, Rizzo AA, Howes RA, Buckwalter DK, et al. Psychological factors and hyperemesis gravidarum. Journal of women's health & gender-based medicine. 2001;10(5):471-7.

79.   Kramer J, Bowen A, Stewart N, Muhajarine N. Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. MCN The American journal of maternal child nursing. 2013;38(1):21-7.

80.   Tan PC, Vani S, Lim BK, Omar SZ. Anxiety and depression in hyperemesis gravidarum: prevalence, risk factors and correlation with clinical severity. Eur J Obstet Gyn R B. 2010;149(2):153-8.

81.   Seng JS, Oakley DJ, Sampselle CM, Killion C, Graham-Bermann S, Liberzon I. Posttraumatic stress disorder and pregnancy complications. Obstetrics & Gynecology. 2001;97(1):17-22.

82.   Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing / Sigma Theta Tau. 2003;35(2):119-25.
83.   Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with pregnancy outcome. Am J Obstet Gynecol. 1986;155(5):1017-22.
84.   Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG. 2011;118(11):1302-13.
85.   Vandraas K, Vikanes Å, Vangen S, Magnus P, Støer N, Grjibovski A. Hyperemesis gravidarum and birth outcomes—a population-based cohort study of 2.2 million births in the Norwegian Birth Registry. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(13):1654-60.
86.   Vikanes ÅV, Støer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy outcomes in the Norwegian mother and child cohort–a cohort study. BMC pregnancy and childbirth. 2013;13(1):169.
87.   Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstet Gynecol. 2006;107(2 Pt 1):285-92.
88.   Stokke G, Gjelsvik BL, Flaatten KT, Birkeland E, Flaatten H, Trovik J. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10-year retrospective cohort study. Acta obstetricia et gynecologica Scandinavica. 2015;94(4):359-67.
89.   Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011;70(2):141-5.
90.   Fejzo MS, Magtira A, Schoenberg FP, Macgibbon K, Mullin PM. Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum. Eur J Obstet Gyn R B. 2015;189:79-84.
91.   Mullin P, Bray A, Schoenberg F, MacGibbon K, Romero R, Goodwin TM, et al. Prenatal exposure to hyperemesis gravidarum linked to increased risk of psychological and behavioral disorders in adulthood. Journal of developmental origins of health and disease. 2011;2(04):200-4.
92.   Ayyavoo A, Derraik JG, Hofman PL, Biggs J, Bloomfield FH, Cormack BE, et al. Severe hyperemesis gravidarum is associated with reduced insulin sensitivity in the offspring in childhood. The Journal of Clinical Endocrinology & Metabolism. 2013;98(8):3263-8.
93.   Vandraas KF, Vikanes ÅV, Støer NC, Troisi R, Stephansson O, Sørensen HT, et al. Hyperemesis gravidarum and risk of cancer in offspring, a Scandinavian registry-based nested case–control study. BMC cancer. 2015;15(1):398.
94.   Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? BJOG. 2008;115(12):1484-93.
95.   Clark S, Hughes B, McDonald SS. The impact of nausea and vomiting of pregnancy on quality of life: Report of a national consumer survey and recommendations for improving care. Obstet Gynecol Surv. 2013;68(9 SUPPL. 1):S1-S10.
96.   O'Brien B, Evans M, White-McDonald E. Isolation from "being alive": coping with severe nausea and vomiting of pregnancy. Nurs Res. 2002;51(5):302-8.
97.   Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol. 2001;22(1):7-12.
98.   Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. Journal of perinatology : official journal of the California Perinatal Association. 2011;31(1):10-20.
99.   Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. Am J Perinatol. 2000;17(4):207-18.
100.   Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. The Lancet Neurology. 2007;6(5):442-55.
101.   Bergin P, Harvey P. Wernicke's encephalopathy and central pontine myelinolysis associated with hyperemesis gravidarum. BMJ. 1992;305(6852):517-8.

102.   Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. Neurology. 1985;35(10):1466-.

103.   Robinson JN, Banerjee R, Thiet MP. Coagulopathy secondary to vitamin K deficiency in hyperemesis gravidarum. Obstet Gynecol. 1998;92(4 Pt 2):673-5.

104.   Hod M, Orvieto R, Kaplan B, Friedman S, Ovadia J. Hyperemesis gravidarum. A review. J Reprod Med. 1994;39(8):605-12.

105.   Vikanes A. Causes of hyperemesis gravidarum: PhD thesis, University of Oslo, Norway; 2010.

106.   Olsen KK. (2004) Gravid kvinne døde etter feilernæring (in Norwegian). English: Pregnant woman died from malnutrition . Aftenposten. (Accessed 09 January 2016).
http://www.aftenposten.no/nyheter/iriks/Gravid-kvinne-dode-etter-feilernaring-6308198.html.

107.   Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. Curr Med Res Opin. 2007;23(4):833-40.

108.   Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(2):e149-60.

109.   Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, et al. Hospitalizations during pregnancy among managed care enrollees. Obstetrics & Gynecology. 2002;100(1):94-100.

110.   Adams MM, Harlass FE, SARNO AP, READ JA, Rawlings JS. Antenatal hospitalization among enlisted servicewomen, 1987-1990. Obstetrics & Gynecology. 1994;84(1):35-9.

111.   Neutel CI. Variation in rates of hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada. In: Koren G, editor. Nausea and Vomiting of Pregnancy : State of the Art 2000. Toronto, Canada: Motherisk; 2000.

112.   Madjunkova S, Maltepe C, Koren G. The delayed-release combination of doxylamine and pyridoxine (Diclegis®/Diclectin®) for the treatment of nausea and vomiting of pregnancy. Pediatric Drugs. 2014;16(3):199-211.

113.   Koren G, Maltepe C. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. Journal of Obstetrics & Gynecology. 2004;24(5):530-3.

114.   Maltepe C, Koren G. Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial. Obstet Gynecol Int. 2013;2013.

115.   Hesketh PJ. Chemotherapy-induced nausea and vomiting. New Engl J Med. 2008;358(23):2482-94.

116.   Priesol AJ. (2014) Motion sickness. UpToDate. (Accessed 02 December 2015).
http://www.uptodate.com/contents/motion-sickness?source=machineLearning&search=nausea+motion+sickness&selectedTitle=1%7E150&sectionRank=2&anchor=H8#H8.

117.   Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Determinants of early medical management of nausea and vomiting of pregnancy. Birth. 2009;36(1):70-7.

118.   Jednak MA, Shadigian EM, Kim MS, Woods ML, Hooper FG, Owyang C, et al. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1999;277(4):G855-G61.

119.   Haugen M, Vikanes Å, Brantsæter AL, Meltzer HM, Grjibovski AM, Magnus P. Diet before pregnancy and the risk of hyperemesis gravidarum. British journal of nutrition. 2011;106(04):596-602.

120.   Bischoff SC, Renzer C. Nausea and nutrition. Autonomic Neuroscience. 2006;129(1):22-7.

121.   Koren G, Maltepe C. How to Survive Morning Sickness Successfully. In: Motherisk, editor.: Motherisk; 2013.

122.   Blumenthal M, editor. The ABC Clinical Guide to Herbs. New York: American Botanical Council/Thieme; 2003.

123.   Forster DA, Denning A, Wills G, Bolger M, McCarthy E. Herbal medicine use during pregnancy in a group of Australian women. BMC Pregnancy Childbirth. 2006;6:21.

124.   Holst L, Wright D, Haavik S, Nordeng H. The use and the user of herbal remedies during pregnancy. J Altern Complement Med. 2009;15(7):787-92.

125.   Nordeng H, Havnen GC. Impact of socio-demographic factors, knowledge and attitude on the use of herbal drugs in pregnancy. Acta Obstet Gynecol Scand. 2005;84(1):26-33.

126.   Pertz HH, Lehmann J, Roth-Ehrang R, Elz S. Effects of Ginger Constituents on the Gastrointestinal Tract: Role of Cholinergic M(3) and Serotonergic 5-HT(3) and 5-HT(4) Receptors. Planta Med. 2011;77(10):973-8.

127.   Lumb AB. Mechanism of antiemetic effect of ginger. Anaesthesia. 1993;48(12):1118.

128.   Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. Obstet Gynecol. 2001;97(4):577-82.

129.   Keating A, Chez RA. Ginger syrup as an antiemetic in early pregnancy. Alternative therapies in health and medicine. 2002;8(5):89-91.

130.   Sripramote M, Lekhyananda N. A randomized comparison of ginger and vitamin B6 in the treatment of nausea and vomiting of pregnancy. J Med Assoc Thai. 2003;86(9):846-53.

131.   Smith C, Crowther C, Willson K, Hotham N, McMillian V. A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. Obstet Gynecol. 2004;103(4):639-45.

132.   Willetts KE, Ekangaki A, Eden JA. Effect of a ginger extract on pregnancy-induced nausea: a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2003;43(2):139-44.

133.   Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 1991;38(1):19-24.

134.   Ensiyeh J, Sakineh MA. Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: a randomised controlled trial. Midwifery. 2008.

135.   Pongrojpaw D, Somprasit C, Chanthasenanont A. A randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy. J Med Assoc Thai. 2007;90(9):1703-9.

136.   Chittumma P, Kaewkiattikun K, Wiriyasiriwach B. Comparison of the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in early pregnancy: a randomized double-blind controlled trial. J Med Assoc Thai. 2007;90(1):15-20.

137.   Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. J Altern Complement Med. 2009;15(3):243-6.

138.   Saberi F, Sadat Z, Abedzadeh-Kalahroudi M, Taebi M. Acupressure and ginger to relieve nausea and vomiting in pregnancy: a randomized study. Iranian Red Crescent Medical Journal. 2013;15(9):854.

139.   Saberi F, Sadat Z, Abedzadeh-Kalahroudi M, Taebi M. Effect of Ginger on Relieving Nausea and Vomiting in Pregnancy: A Randomized, Placebo-Controlled Trial. Nursing and Midwifery Studies. 2014;3(1).

140.   Biswas SC, Dey R, Kamliya GS, Bal R, Hazra A, Tripathi SK. A single-masked, randomized, controlled trial of ginger extract in the treatment of nausea and vomiting of pregnancy. J Int Med Sci Acad. 2011;24(4):167-9.

141.   Mohammadbeigi R, Shahgeibi S, Soufizadeh N, Rezaiie M, Farhadifar F. Comparing the effects of ginger and metoclopramide on the treatment of pregnancy nausea. Pak J Biol Sci. 2011;14(16):817-20.

142.   Thomson M, Corbin R, Leung L. Effects of ginger for nausea and vomiting in early pregnancy: a meta-analysis. The Journal of the American Board of Family Medicine. 2014;27(1):115-22.

143.   Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014;13:20.

144.   Matthews A, Haas DM, O'Mathuna DP, Dowswell T, Doyle M. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2014;3:CD007575.

145.   Goldstein L, Berkovitch M. Antiemetics. In: Schaefer C, Peters P, Miller R, editors. Drugs During Pregnancy and Lactation. 2nd ed. London: Elsevier; 2007. p. 82-3.

146.   Mills E, Duguoa JJ, Perri D, Koren G. Herbal medicines in pregnancy and lactation: An evidence-based approach. London ; New York: Taylor & Francis; 2006.
147.   Tiran D. Ginger to reduce nausea and vomiting during pregnancy: Evidence of effectiveness is not the same as proof of safety. Complement Ther Clin Pract. 2012;18(1):22-5.
148.   Westfall RE. Use of anti-emetic herbs in pregnancy: women's choices, and the question of safety and efficacy. Complement Ther Nurs Midwifery. 2004;10(1):30-6.
149.   Srivastava KC. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism. Biomed Biochim Acta. 1984;43(8-9):S335-46.
150.   Bordia A, Verma SK, Srivastava KC. Effect of ginger (Zingiber officinale Rosc.) and fenugreek (Trigonella foenumgraecum L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids. 1997;56(5):379-84.
151.   Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2005;59(4):425-32.
152.   Srivastava KC. Effect of onion and ginger consumption on platelet thromboxane production in humans. Prostaglandins Leukotrienes Essent Fatty Acids. 1989;35(3):183-5.
153.   Backon J. Ginger in preventing nausea and vomiting of pregnancy; a caveat due to its thromboxane synthetase activity and effect on testosterone binding. Eur J Obstet Gynecol Reprod Biol. 1991;42(2):163-4.
154.   Portnoi G, Chng LA, Karimi-Tabesh L, Koren G, Tan MP, Einarson A. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol. 2003;189(5):1374-7.
155.   Gill SK, Maltepe C, Koren G. The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy. Canadian Journal of Gastroenterology. 2009;23(4):270.
156.   Dean CR, O'Hara ME. Ginger is ineffective for hyperemesis gravidarum and causes harm: an internet based survey of suffers. First World Colloquium on Hyperemesis Gravidarum in Bergen, Norway, 20-21 October. 2015.
157.   Zahra B, Mehrdad K, Atena S-R. The effect of ginger biscuit on nausea and vomiting in early pregnancy. Acta Medica Iranica. 2009;47(1):51-6.
158.   Roscoe JA, Matteson SE. Acupressure and acustimulation bands for control of nausea: a brief review. Am J Obstet Gynecol. 2002;186(5):S244-S7.
159.   Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstetrics & Gynecology. 1991;78(1):33-6.
160.   Vutyavanich T, Wongtra-ngan S, Ruangsri R-a. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 1995;173(3):881-4.
161.   Wibowo N, Purwosunu Y, Sekizawa A, Farina A, Tambunan V, Bardosono S. Vitamin B-6 supplementation in pregnant women with nausea and vomiting. Int J Gynecol Obstet. 2012;116(3):206-10.
162.   McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology. 1994;50(1):27-37.
163.   Axelsson P, Futtrup TB, Buchgreitz L, Høltzermann M, Martinsen AW, Odgaard HS, et al. Hyperemesis gravidarum - guideline. Dansk Selskab for Obstestrik og Gynækologi (in Danish). English: Danish Society for Obstetrics and Gynaecology; 2013.
164.   Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol. 1997;14(3):119-24.
165.   Chin J, Gregor S, Persaud N. Re-analysis of Safety Data Supporting Doxylamine Use for Nausea and Vomiting of Pregnancy. American journal of perinatology. 2014;31(8):701-10.
166.   Asker C, Norstedt Wikner B, Kallen B. Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol. 2005;61(12):899-906.

167.   Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and nonpharmacological treatments for nausea and vomiting of pregnancy. Drugs. 2000;59(4):781-800.
168.   Gilboa SM, Strickland MJ, Olshan AF, Werler MM, Correa A. Use of antihistamine medications during early pregnancy and isolated major malformations. Birth Defects Research Part A: Clinical and Molecular Teratology. 2009;85(2):137-50.
169.   Gilboa SM, Ailes EC, Rai RP, Anderson JA, Honein MA. Antihistamines and birth defects: a systematic review of the literature. Expert opinion on drug safety. 2014;13(12):1667-98.
170.   Kallen B, Mottet I. Delivery outcome after the use of meclozine in early pregnancy. Eur J Epidemiol. 2003;18(7):665-9.
171.   Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):571. e1-. e7.
172.   Koren G, Clark S, Hankins GD, Caritis SN, Umans JG, Miodovnik M, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. BMC pregnancy and childbirth. 2015;15(1):59.
173.   WHO Collaborating Centre for Drugs Statistics Methodology. (2013) Guidelines for ATC classification and DDD assignment 2013. (Accessed 19 March 2013).
http://www.whocc.no/atc_ddd_index/
174.   Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol. 2010;115(5):975-81.
175.   Pasternak B, Svanstrom H, Molgaard-Nielsen D, Melbye M, Hviid A. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. JAMA : the journal of the American Medical Association. 2013;310(15):1601-11.
176.   Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. New Engl J Med. 2009;360(24):2528-35.
177.   Abas MN, Tan PC, Azmi N, Omar SZ. Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstetrics & Gynecology. 2014;123(6):1272-9.
178.   Kashifard M, Basirat Z, Golsorkhtabar-Amiri M, Moghaddamnia A. Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study. Clinical and experimental obstetrics & gynecology. 2012;40(1):127-30.
179.   Bsat FA, Hoffman DE, Seubert DE. Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy. Journal of perinatology. 2003;23(7):531-5.
180.   Klauser CK, Fox NS, Istwan N, Rhea D, Rebarber A, Desch C, et al. Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications. American journal of perinatology. 2011;28(9):715-21.
181.   Lombardi D, Istwan N, Rhea D, O'Brien J, Barton J. Measuring outpatient outcomes of emesis and nausea management in pregnant women. Managed care (Langhorne, Pa). 2004;13(11):48-52.
182.   Milkovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. Am J Obstet Gynecol. 1976;125(2):244-8.
183.   Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. Am J Obstet Gynecol. 1977;128(5):486-8.
184.   Gill SK, Einarson A. The safety of drugs for the treatment of nausea and vomiting of pregnancy. Expert Opin Drug Saf. 2007;6(6):685-94.
185.   Briggs GG, Freeman RK. Drugs in Pregnancy and Lactation. 10th ed. London: Wolters Kluwer; 2015.
186.   Reis M, Källén B. Maternal use of antipsychotics in early pregnancy and delivery outcome. Journal of clinical psychopharmacology. 2008;28(3):279-88.

187.   Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophrenia bulletin. 2010;36(3):518-44.

188.   Teahon K. Nausea and vomiting. In: Walker R, Edwards C, editors. Clinical Pharmacy and Therapeutics. 3rd ed. London: Churchill Livingstone.

189.   European Medicines Agency. (2013) European Medicines Agency recommends changes to the use of metoclopramide. European Medicines Agency. (Accessed 19 March 2015). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146614 .pdf.

190.   U.S. Food and Drug Administration. (2010) Safety information - Reglan (metoclopramide) tablets, ODT (Orally Disintegrating Tablets), and injection. (Accessed 08 July 2015). http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm.

191.   Rao A, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Alimentary pharmacology & therapeutics. 2010;31(1):11-9.

192.   Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51. e1-. e8.

193.   Koren G. Scary Science: Ondansetron Safety in Pregnancy-Two Opposing Results From the Same Danish Registry. Therapeutic drug monitoring. 2014;36(1):1-2.

194.   Andersen JT, Jimenez-Solem E, Andersen NL, Poulsen HE. Ondansetron use in early pregnancy and the risk of congenital malformations-a register based nationwide cohort study. Pharmacoepidemiol Drug Saf. 2013;22:13-4.

195.   Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. The New England journal of medicine. 2013;368(9):814-23.

196.   Danielsson B, Wikner BN, Källén B. Use of ondansetron during pregnancy and congenital malformations in the infant. Reprod Toxicol. 2014;50:134-7.

197.   Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth defects research Part A, Clinical and molecular teratology. 2012;94(1):22-30.

198.   Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstetrics & Gynecology. 2014;124(4):735-42.

199.   Koren G, Maltepe C, Madjunkova S. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstet Gynecol. 2015;125(2):490.

200.   U.S. Food and Drug Administration. (2011) Drug safety communication: Abnormal heart rythms may be associated with use of Zofran (ondansetron) (Accessed 19 March 2015). http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm.

201.   Safari HR, Fassett MJ, Souter IC, Alsulyman OM, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. Am J Obstet Gynecol. 1998;179(4):921-4.

202.   Yost NP, McIntire DD, Wians FH, Jr., Ramin SM, Balko JA, Leveno KJ. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. Obstet Gynecol. 2003;102(6):1250-4.

203.   Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, et al. First trimester exposure to corticosteroids and oral clefts. Birth defects research Part A, Clinical and molecular teratology. 2003;67(12):968-70.

204.   Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62(6):385-92.

205.   Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, et al. Update on new developments in the study of human teratogens. Teratology. 2002;65(4):153-61.

206.   Rodríguez-Pinilla E, Luisa Martínez-Frías M. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology. 1998;58(1):2-5.

207.   Holmgren C, Aagaard-Tillery KM, Silver RM, Porter TF, Varner M. Hyperemesis in pregnancy: an evaluation of treatment strategies with maternal and neonatal outcomes. Am J Obstet Gynecol. 2008;198(1):56. e1-. e4.

208.   Gill SK, Maltepe C, Mastali K, Koren G. The effect of Acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. Obstet Gynecol Int. 2009;2009:585269.

209.   Gill SK, O'Brien L, Koren G. The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis. Dig Dis Sci. 2009;54(9):1835-8.

210.   Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. New Engl J Med. 2010;363(22):2114-23.

211.   Chou F-H, Avant KC, Kuo S-H, Fetzer SJ. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning, and psychosocial adaptation in a sample of mothers: a questionnaire survey. International Journal of Nursing Studies. 2008;45(8):1185-91.

212.   Abedian Z, Abbaszadeh N, Latifnejad Roudsari R, Taghi Shakeri M. The Effects of Telephone Support on Stress and Perceived Social Support in Primiparous Women Experiencing Nausea and Vomiting in the First Half of Pregnancy. Journal of Midwifery and Reproductive Health. 2015;3(2):328-34.

213.   Liu M-C, Kuo S-H, Lin C-P, Yang Y-M, Chou F-H, Yang Y-H. Effects of Professional Support on Nausea, Vomiting, and Quality of Life During Early Pregnancy. Biological research for nursing. 2013:1099800413506036.

214.   Gadsby R, Barnie-Adshead AM. Severe nausea and vomiting of pregnany: should it be treated with appropriate pharmacotherapy? The Obstetrician & Gynaecologist. 2011;13:107-11.

215.   Munch S. A qualitative analysis of physician humanism: women's experiences with hyperemesis gravidarum. Journal of perinatology : official journal of the California Perinatal Association. 2000;20(8 Pt 1):540-7.

216.   Locock L, Alexander J, Rozmovits L. Women's responses to nausea and vomiting in pregnancy. Midwifery. 2008;24(2):143-52.

217.   Wood H, McKellar LV, Lightbody M. Nausea and vomiting in pregnancy: blooming or bloomin' awful? A review of the literature. Women and birth : journal of the Australian College of Midwives. 2013;26(2):100-4.

218.   Hardy JR, Leaderer BP, Holford TR, Hall GC, Bracken MB. Safety of medications prescribed before and during early pregnancy in a cohort of 81 975 mothers from the UK General Practice Research Database. Pharmacoepidemiol Drug Saf. 2006;15(8):555-64.

219.   Markl GE, Strunz-Lehner C, Egen-Lappe V, Hasford J. Prescribing patterns of anti-emetic drugs during pregnancy in Germany. Archives of gynecology and obstetrics. 2007;275(6):461-7.

220.   Naumann CR, Zelig C, Napolitano PG, Ko CW. Nausea, vomiting, and heartburn in pregnancy: a prospective look at risk, treatment, and outcome. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2012;25(8):1488-93.

221.   Berard A, Sheehy O. The Quebec Pregnancy Cohort--prevalence of medication use during gestation and pregnancy outcomes. PLoS One. 2014;9(4):e93870.

222.   De Vigan C, De Walle HEK, Cordier S, Goujard J, Knill-Jones R, Ayme S, et al. Therapeutic drug use during pregnancy: A comparison in four European countries. J Clin Epidemiol. 1999;52(10):977-82.

223.   Hollyer T, Boon H, Georgousis A, Smith M, Einarson A. The use of CAM by women suffering from nausea and vomiting during pregnancy. BMC Complement Altern Med. 2002;2:5.

224.   Mazzotta P, Maltepe C, Navioz Y, Magee L, Koren G. Attitudes, management and consequences of nausea and vomiting of pregnancy in the United States and Canada. Int J Gynecol Obstet. 2000;70(3):359-65.

225.   Einarson A, Koren G, Bergman U. Nausea and vomiting in pregnancy: a comparative European study. Eur J Obstet Gynecol Reprod Biol. 1998;76(1):1-3.
226.   Goodwin TM, Poursharif B, Korst LM, MacGibbon KW, Romero R, Fejzo MS. Secular trends in the treatment of hyperemesis gravidarum. Am J Perinatol. 2008;25(3):141-7.
227.   WHO International Working Group for Drug Statistics Methodology/ WHO Collaborating Centre for Drug Statistics Methodology/ WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. Introduction to drug utilization research. Geneva: World Health Organization; 2003.
228.   Strom BL, Kimmel SE, editors. Textbook of Pharmacoepidemiology. Chichester: John Wiley & Sons Ltd.; 2006.
229.   Rothman KJ. Epidemiology. New York: Oxford University Press; 2012.
230.   Pope C, Mays N, editors. qualitative reseach in health care. 3rd ed. Oxford: Blackwell Publishing 2006.
231.   Smith F. Research Methods in Pharmacy Practice. London: Pharmaceutical Press; 2002.
232.   Devers KJ. How will we know" good" qualitative research when we see it? Beginning the dialogue in health services research. Health services research. 1999;34(5 Pt 2):1153.
233.   Armstrong D, Gosling A, Weinman J, Marteau T. The place of inter-rater reliability in qualitative research: an empirical study. Sociology. 1997;31(3):597-606.
234.   Mays N, Pope C. Qualitative research: rigour and qualitative research. Bmj. 1995;311(6997):109-12.
235.   Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol. 2006;35(5):1146-50.
236.   Norwegian Institute of Public Health. (2010) What is the the Norwegian Mother and Child Cohort Study. . (Accessed 05 November 2015).
http://www.fhi.no/eway/default.aspx?pid=240&trg=MainContent_6894&Main_6664=6894:0:25,7372:1:0:0:::0:0&MainContent_6894=6706:0:25,7373:1:0:0:::0:0.
237.   Norwegian Institute of Public Health. The Norwegian Mother and Child Cohort Study. (Accessed 09 January 2016).
http://www.fhi.no/eway/default.aspx?pid=240&trg=Main_6664&Main_6664=6894:0:25,7372:1:0:0:::0:0.
238.   Norwegian Institute of Public Health. The Nowegian Mother and Child Cohort Study. Questionnaire 1. Norwegian Institute of Public Health,. (Accessed 05 November 2015).
http://www.fhi.no/dokumenter/1f32a49514.pdf.
239.   Norwegian Institute of Public Health. The Nowegian Mother and Child Cohort Study. Questionnaire 3. Norwegian Institute of Public Health,. (Accessed 05 November 2015).
http://www.fhi.no/dokumenter/7b6b32b0cd.pdf.
240.   Norwegian Institute of Public Health. The Nowegian Mother and Child Cohort Study. Questionnaire 4. Norwegian Institute of Public Health,. (Accessed 05 November 2015).
http://www.fhi.no/dokumenter/9ecca1c459.pdf.
241.   Nowegian Institute of Public Health. (2010) Questionnaires from MoBa. Nowegian Institute of Public Health. (Accessed 05 November 2015).
http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3138:1:0:0:::0:0.
242.   Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand. 2000;79(6):435-9.
243.   Norwegian Institute of Public Health. (2012) Medical Birth Registry of Norway (MBRN). Norwegian Institute of Public Health. (Accessed 05 November 2015).
http://www.fhi.no/eway/default.aspx?pid=240&trg=Main_6664&Main_6664=6898:0:25,7840:1:0:0:::0:0.
244.   Norwegian Institute of Public Health. (2012) Medical Birth Registry of Norway. (Accessed 15 December 2015). http://www.fhi.no/artikler/?id=94819

245.	Norwegian Institute of Public Health. (2012) Notification of birth to the Medical Birth Registry of Norway. (Accessed 15 December 2015). http://www.fhi.no/artikler/?id=94820.
246.	Norwegian Institute of Public Health. (2011) Definisjonsrapporter for variabler i Medisinsk fødselsregister (in Norwegian). English: Definition reports for variables in the Medical Birth Registry of Norway. (Accessed 05 January 2016). http://www.fhi.no/dokumenter/8105c63e8e.pdf.
247.	European Surveillance of Congenital Anomalies. (2014) Guide 1.4, Chapter 3.3. EUROCAT Subgroups of Congenital Anomalies (Version 2014; implemented in EDMP December 2014, used for website prevalence tables from December 2014). (Accessed 08 January 2016). http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.3.pdf.
248.	Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. The British journal of psychiatry : the journal of mental science. 1987;150:782-6.
249.	Cox JL, Holden J. Perinatal mental health: a guide to the Edinburgh Postnatal Depression Scale (EPDS): RCPsych Publications; 2003.
250.	Bergink V, Kooistra L, Lambregtse-van den Berg MP, Wijnen H, Bunevicius R, van Baar A, et al. Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res. 2011;70(4):385-9.
251.	Department of Health. Edinburgh Postnatal Depression Scale (EPDS): Translated versions – validated. Perth, Western Australia: State Perinatal Mental Health Reference Group. 2006.
252.	Grote V, Vik T, von Kries R, Luque V, Socha J, Verduci E, et al. Maternal postnatal depression and child growth: a European cohort study. BMC pediatrics. 2010;10:14.
253.	Stewart DE, Gagnon A, Saucier JF, Wahoush O, Dougherty G. Postpartum depression symptoms in newcomers. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2008;53(2):121-4.
254.	Tamminen T. Postnatal depression, breastfeeding and mother-infant interaction. Unpublished doctoral thesis. Tampere, Finland: University of Tampere; 1990.
255.	Malterud K. Systematic text condensation: a strategy for qualitative analysis. Scand J Public Health. 2012;40(8):795-805.
256.	Koren G, Piwko C, Ahn E, Boskovic R, Maltepe C, Einarson A, et al. Validation studies of the Pregnancy Unique-Quantification of Emesis (PUQE) scores. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2005;25(3):241-4.
257.	Birkeland E, Stokke G, Tangvik RJ, Torkildsen EA, Boateng J, Wollen AL, et al. Norwegian PUQE (Pregnancy-Unique Quantification of Emesis and Nausea) Identifies Patients with Hyperemesis Gravidarum and Poor Nutritional Intake: A Prospective Cohort Validation Study. PloS one. 2015;10(4).
258.	Norwegian Institute of Public Health. (2015) MoBa - in brief. (Accessed 12 January 2016). http://www.fhi.no/dokumenter/b64e754300.pdf.
259.	Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol. 2009;23(6):597-608.
260.	Moussally K, Oraichi D, Berard A. Herbal products use during pregnancy: prevalence and predictors. Pharmacoepidemiol Drug Saf. 2009;18(6):454-61.
261.	Heitmann K. Use of and attitudes to use of herbal medicines during pregnancy. Master's thesis. . Bergen: University of Bergen; 2009.
262.	Barnes J, Anderson L, Phillipson J. Herbal Medicines. Third ed. London: Pharmaceutical Press; 2007.
263.	Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004;6(3):e34.
264.	van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? American journal of epidemiology. 2010;172(11):1292-8.

265.   Ekman A, Dickman PW, Klint A, Weiderpass E, Litton JE. Feasibility of using web-based questionnaires in large population-based epidemiological studies. Eur J Epidemiol. 2006;21(2):103-11.
266.   Whitehead L. Methodological issues in Internet-mediated research: a randomized comparison of internet versus mailed questionnaires. J Med Internet Res. 2011;13(4):e109.
267.   Ritter P, Lorig K, Laurent D, Matthews K. Internet versus mailed questionnaires: a randomized comparison. J Med Internet Res. 2004;6(3):e29.
268.   Touvier M, Mejean C, Kesse-Guyot E, Pollet C, Malon A, Castetbon K, et al. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. Eur J Epidemiol. 2010;25(5):287-96.
269.   van Gelder MM, Schouten NP, Merkus PJ, Verhaak CM, Roeleveld N, Roukema J. Using Web-Based Questionnaires and Obstetric Records to Assess General Health Characteristics Among Pregnant Women: A Validation Study. Journal of medical Internet research. 2015;17(6).
270.   van Gelder M, Pijpe A. E-epidemiology: a comprehensive update. Cancer. 2013;15:0.007.
271.   Ekman A, Litton J-E. New times, new needs; e-epidemiology. Eur J Epidemiol. 2007;22(5):285-92.
272.   O'Higgins A, Murphy OC, Egan A, Mullaney L, Sheehan S, Turner M. The use of digital media by women using the maternity services in a developed country. Irish medical journal. 2013;107(10):313-5.
273.   Bert F, Gualano MR, Brusaferro S, De Vito E, de Waure C, La Torre G, et al. Pregnancy e-health: a multicenter Italian cross-sectional study on Internet use and decision-making among pregnant women. Journal of epidemiology and community health. 2013:jech-2013-202584.
274.   Seybert H. (2011) Internet use in households and by individuals in 2011. . Eurostat Statistics in focus. (Accessed 19 March 2015).
http://ec.europa.eu/eurostat/documents/3433488/5579964/KS-SF-11-066-EN.PDF/090e071f-c3a9-45d8-aa90-9b142251fd3a?version=1.0
275.   Usage and population statistics. [Internet]. 2012 (Accessed 19 March 2015). Available from: http://www.internetworldstats.com/.
276.   Household Use of Information Technology, Australia, 2010-11. [Internet]. 2010 (Accessed 03 February 2014). Available from:
http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/8146.0MainFeatures12010-11?opendocument&tabname=Summary&prodno=8146.0&issue=2010-11&num=&view=.
277.   Individual Internet use and E-commerce (2010) [Internet]. 2011 (Accessed 03 February 2014). Available from: http://www.statcan.gc.ca/daily-quotidien/111012/dq111012a-eng.htm.
278.   The 2012 Statistical Abstract. Information & Communications. [Internet]. 2010 (Accessed 19 March 2015). Available from:
http://www2.census.gov/library/publications/2011/compendia/statab/131ed/2012-statab.pdf.
279.   Norwegian media barometer - Table: 04519: Percentage internet users and minutes used for internet an average day, by sex and education [Internet]. Statistics Norway,. 2015 (Accessed 08 July 2015). Available from:
https://www.ssb.no/statistikkbanken/selecttable/hovedtabellHjem.asp?KortNavnWeb=medie&CMSSubjectArea=kultur-og-fritid&PLanguage=1&checked=true.
280.   Koren G, Maltepe C, Navioz Y, Wolpin J. Recall bias of the symptoms of nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2004;190(2):485-8.
281.   Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Epidemiology of nausea and vomiting of pregnancy: prevalence, severity, determinants, and the importance of race/ethnicity. BMC Pregnancy Childbirth. 2009;9:26.
282.   Spek V, Nyklíček I, Cuijpers P, Pop V. Internet administration of the Edinburgh depression scale. Journal of affective disorders. 2008;106(3):301-5.
283.   Malterud K. Kvalitative metoder i medisinsk forskning. En innføring. (in Norwegian) English: Qualitative methods in medical reasearch. An introduction. 3rd ed. Oslo: Universitetsforlaget; 2011.

284. Morgan DL. Focus groups as qualitative research. 2nd ed. Thousand Oaks: Sage Publications; 1997. 80 p.
285. Smith F. Reasearch Methods in Pharmacy Practice. London: Pharmaceutical Press; 2002.
286. Poland BD. Transcription quality as an aspect of rigor in qualitative research. Qualitative inquiry. 1995;1(3):290-310.
287. Mays N, Pope C. Qualitative research in health care: Assessing quality in qualitative research. BMJ: British Medical Journal. 2000;320(7226):50.
288. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth. 1992;19(3):138-43.
289. Gadsby R, Barnie-Adshead T, Sykes C. Why won't doctors prescribe antiemetics in pregnancy? BMJ. 2011;343:d4387.
290. Gadsby R. Commentary: General practitioners are wary of treating sickness in pregnancy. Brit Med J. 2004;328(7438):505-6.
291. Mazzotta P, Magee LA, Maltepe C, Lifshitz A, Navioz Y, Koren G. The perception of teratogenic risk by women with nausea and vomiting of pregnancy. Reprod Toxicol. 1999;13(4):313-9.
292. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66(2):207-14.
293. Odalovic M, Kovacevic SV, Nordeng H, Ilic K, Sabo A, Tasic L. Predictors of the use of medications before and during pregnancy. International journal of clinical pharmacy. 2013;35(3):408-16.
294. Sharashova EE, Anda EE, Grjibovski AM. Early pregnancy body mass index and spontaneous preterm birth in Northwest Russia: a registry-based study. BMC Pregnancy Childbirth. 2014;14:303.
295. Odalovic M, Vezmar Kovacevic S, Ilic K, Sabo A, Tasic L. Drug use before and during pregnancy in Serbia. International Journal of Clinical Pharmacy. 2012;34(5):719-27.
296. Frawley J, Adams J, Sibbritt D, Steel A, Broom A, Gallois C. Prevalence and determinants of complementary and alternative medicine use during pregnancy: results from a nationally representative sample of Australian pregnant women. Aust N Z J Obstet Gynaecol. 2013;53(4):347-52.
297. Holst L, Nordeng H, Haavik S. Use of herbal drugs during early pregnancy in relation to maternal characteristics and pregnancy outcome. Pharmacoepidemiol Drug Saf. 2008;17(2):151-9.
298. The Finnish Food Safety Authority Evira. (2010) Warning label to be added on food supplements containing ginger as well as on ginger tea, and corresponding drink powders. Evira. (Accessed 18 November 2015).
http://www.evira.fi/portal/en/food/manufacture+and+sales/labelling/warning+labelling+and+instructions+for+use/warning+label+to+be+added+on+food+supplements+containing+ginger+as+well+as+on+ginger+tea++and+corresponding+drink+powders.
299. Nordeng H, Havnen GC. Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiol Drug Saf. 2004;13(6):371-80.
300. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol. 2006;20(4):270-8.
301. European Medicines Agency. Herbal medicinal products. European Medicines Agency. (Accessed 8 December 2015).
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000208.jsp&mid=WC0b01ac05800240cf.
302. The Medicines Agency of Norway. Hva er et legemiddel? (in Norwegian). English: What is a medicine? The Medicines Agency of Norway. (Accessed 8 December 2015).
http://www.legemiddelverket.no/Godkjenning_og_regelverk/Klassifisering/Hva_er_et_legemiddel/Sider/default.aspx.
303. The Medicines Agency of Norway. Tradisjonelle og veletablerte plantebaserte legemidler med markedsføringstillatelse (in Norwegian). English: Herbal medicinal products with traditional and well-established use with marketing authorisation. The Medicines Agency of Norway.

(Accessed 8 December 2015).
http://www.legemiddelverket.no/Godkjenning_og_regelverk/godkjenning_av_legemidler/planteba serte_legemidler/Sider/Tradisjonelle-og-veletablerte-plantebaserte-legemidler-med-markedsføringstillatelse.aspx#veletablerte.
304.   Huynh Do ML. Hyperemesis gravidarum i Norge. Legemiddelbehandling, psykososial byrde og erfaringer ved møte med helsetjenesten (in Norwegian). English: Hyperemesis gravidarum in Norway. Medical treatment, psychosocial burden and experiences with health care. Master's thesis. Oslo: University of Oslo; 2015.
305.   Lupattelli A, Spigset O, Nordeng H. Adherence to medication for chronic disorders during pregnancy: results from a multinational study. Int J Clin Pharm. 2014;36(1):145-53.
306.   Jasper JD, Goel R, Einarson A, Gallo M, Koren G. Effects of framing on teratogenic risk perception in pregnant women. Lancet. 2001;358(9289):1237-8.
307.   Einarson A, Selby P, Koren G. Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counselling. J Psychiatry Neurosci. 2001;26(1):44-8.

PAPER II

II

RESEARCH ARTICLE   **Open Access**

CrossMark

Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers

Kristine Heitmann[1*], Lone Holst[1], Angela Lupattelli[2], Caroline Maltepe[3] and Hedvig Nordeng[2,4]

Abstract

Background: The factors related to the treatment of nausea during pregnancy have not yet been investigated in several countries simultaneously. The present study aimed to describe differences in self-reported nausea during pregnancy and the patterns of use for both conventional and herbal medicines across countries. The factors related to nausea and its treatment and the relationships between different self-reported co-morbidities and nausea were also investigated.

Methods: This cross-sectional study used data collected by a web-based questionnaire distributed between October 2011 and February 2012 in several countries within five regions: Western, Northern, and Eastern Europe, North America, and Australia. Women who were pregnant or had a child less than one year old were eligible to participate.

Results: A total of 9113 women were included in the study, whereof 6701 (73.5 %) had experienced nausea during pregnancy. Among respondents with nausea, conventional medicines were used by 1201 (17.9 %) women and herbal medicines by 556 (8.3 %) women. The extent of self-reported nausea and its treatment varied by country. Education, working status, and folic acid use were significantly associated with the use of conventional medicines against nausea. Respondents who had nausea also had a high burden of co-morbidity.

Conclusion: The prevalence of nausea was high across all participating countries but its treatment varied, possibly due to cultural differences and differences in attitudes towards medicines. A high degree of co-morbidity was found among respondents with nausea.

Keywords: Nausea, Pregnancy, Pharmacotherapy, Herbal medicine, Multinational, Internet

Background

Nausea and vomiting during pregnancy (NVP) is one of the most common pregnancy-related complaints, affecting millions of pregnant women worldwide each year. Approximately 7 out of 10 women experience nausea during pregnancy [1] and 50 % experience both nausea and vomiting [2–4]. For most patients, symptoms appear around the sixth week of pregnancy and gradually decline during the second trimester, peaking at 8–13 weeks [2, 3]. However, 10 % of women will still experience symptoms after 20–22 weeks of pregnancy [3, 4]. The most severe form of NVP, hyperemesis gravidarum, is characterised by severe and persistent nausea and vomiting leading to weight loss, ketonuria, nutritional deficiencies, dehydration and electrolyte imbalance, often so severe as merits hospitalisation, and affects about 1.1% of the pregnant women [1].

NVP has been shown to greatly impact a woman's life, negatively affecting daily activities, relationship with partner, parenting, occupation and social functioning [5–7]. Feelings of isolation, fatigue, depression, and helplessness due to nausea have also been described [7–9]. Nausea has been reported to be responsible for 33 % of all sick leave during pregnancy [10]. In the USA and Canada, NVP is a significant economic burden to women and society [11, 12].

Because NVP is often most intense during the first trimester when organogenesis occurs, teratogenic effects

* Correspondence: kristine.heitmann@igs.uib.no
[1]Department of Global Public Health and Primary Care and Centre for Pharmacy, University of Bergen, Bergen, Norway
Full list of author information is available at the end of the article

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 2 of 13

are a concern in treatment. This may lead to caution in prescribing and taking conventional medicines to treat this condition, despite the proven safety of use during pregnancy of many medicines. Pregnant women often overestimate the teratogenic risk associated with the use of medicines in general [13]. Consequently, many women may turn to complementary and alternative medicine (CAM) to alleviate their symptoms or choose to not treat their symptoms due to the fear that taking anything during pregnancy may harm the baby. Despite the high prevalence of NVP, little is known about differences in NVP treatments, i.e. conventional and herbal medicines, across countries. An informal survey in various European countries in 1998 found wide variations in the types of treatment used against mild and moderate nausea and vomiting, whereas hyperemesis gravidarum was treated in a similar fashion in the vast majority of countries [14].

No study has investigated the factors related to NVP treatment in several countries simultaneously. Studies are available from various countries, but data collection methods vary [5, 7, 15–20], making direct comparisons impossible. In addition different therapies have been included in the definition of CAM [15, 16, 18, 19].

New possibilities for uniform data collection in several countries are emerging that are advantageous for the field of e-epidemiology [21, 22]. Large potential gains in well-being for the mother and society as a whole can be achieved with better knowledge on how nausea in pregnancy is being treated. This study is the first to investigate the factors related to the treatment of nausea during pregnancy at a multinational level.

The present study aimed to describe differences in self-reported nausea during pregnancy, as well as the patterns of use of both conventional and herbal medicine across countries in Western, Northern, and Eastern Europe, North America, and Australia. The study also aimed to investigate the factors related to nausea and its treatment, as well as the relationships between different self-reported co-morbidities and nausea.

Methods

This cross-sectional study was based on data from a web-based questionnaire covering nausea, medicines against nausea, herbal medicines against nausea, sociodemographic factors, maternal health, and lifestyle during pregnancy [23]. The online questionnaire was distributed simultaneously in 18 countries: Austria, Australia, Croatia, Canada, France, Finland, Iceland, Italy, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, the Netherlands, United Kingdom, and USA. The original data file consisted of 9459 women, including 346 South American women who accessed the questionnaire via North American websites [23]. For this sub-study, the 346 women from South America were excluded in effort to reduce selection bias as

this was considered a special group of women, resulting in a final study population of 9113 women.

Women who were pregnant or had a child who was less than one year old were eligible to participate in the study. An advert containing a link to the online self-completed questionnaire was posted on commonly visited pregnancy and baby related websites in the participating countries. National coordinators selected the most relevant national websites, social networks, and pregnancy forums [23]. The questionnaire was available for 2 months in each participating country between 1st of October 2011 and 29th of February 2012.

The questionnaire was originally developed in Norwegian and English before being translated into the relevant languages, and is available online as an appendix to the paper by Lupattelli et al. [23]. A pilot study was performed during September 2011 in Norway, Finland, Italy, and Sweden ($n = 47$) but resulted in no major changes to the questionnaire. All national coordinators assured the quality of their version of the questionnaire.

The representativeness of the study population was assessed by comparing the sociodemographic and lifestyle characteristics (i.e., age, marital status, education, and smoking) of the study population to the general birthing population in the corresponding country. The similarities were satisfactory with the exception that the study participants were generally more educated than the general birthing population, as described in detail elsewhere [23].

Measures of nausea, health disorders, and conventional and herbal medicines use during pregnancy

The respondents were presented with a list of questions related to different health disorders/short-term illnesses during pregnancy, including nausea, and asked if they had any of these illnesses. In case of an affirmative response, the respondents were asked about medicine use related to each individual illness. The medicines used were reported in free-text entry fields. The timing of use for both conventional and herbal medicines could also be reported and were defined by the three possible exposure windows included in the questionnaire: weeks 1–12 (first trimester); weeks 13–24 (second trimester), and week 25 to delivery (third trimester). A list of chronic disorders was also presented to the respondents, including cardiovascular and rheumatic disorders, diabetes and epilepsy, and an open-ended option. Furthermore, the women were presented with a question on sick leave during pregnancy (dichotomised yes/no).

In addition to the standardised questions about medicine use for specific illnesses, the respondents were questioned about over-the-counter (OTC) medicine use during pregnancy, including OTC medicines against nausea, and the timing of use. A medicine was defined

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 3 of 13

as a single product containing one or more active ingredients. The main active ingredient(s) and formulation of the branded medicinal product were identified for each specific trademark name and recorded using either the national medicine database or the Martindale textbook [24]. All medicines were then coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes in accordance with the World Health Organization (WHO) ATC index [25]. Whenever possible, the 5th level of the ATC was used.

Any use of herbal medicines was specifically requested, including the name of the product, reason for its use, and the timing of use during pregnancy. The name of the herbal medicine and the reason for its use were reported as free-text entry fields. Herbal medicine could also be reported under the disease-specific questions and the questions about OTC medicine. Herbal medicines were identified by name and coded in accordance with a pre-determined list of herbs [26].

The respondents were classified as having nausea during pregnancy if they reported having had nausea when questioned about short-term illnesses, if they reported any use of OTC medicines against nausea, or if they gave nausea as an indication for the use of herbal or homeopathic medicines.

Sociodemographic and lifestyle variables
The following variables were explored in relation to nausea and the use of conventional medicines: region of residence, maternal age, parity, marital status, education, working status, smoking during pregnancy, use of folic acid, and multiple pregnancy. Sociodemographic variables were categorised as presented in Table 1.

Measurements of maternal mental health
Symptoms of depression were measured by the Edinburgh Postnatal Depression Scale (EPDS), a self-rating 10-item scale initially developed by Cox et al. to detect postnatal depression [27]. However, the scale has also been validated as a screening tool for major depression in pregnant women with satisfactory results and has been used in several studies in various countries [28]. Cut-off scores of 11, 10 and 10 applied at weeks 12, 24, and 36 of pregnancy, respectively, resulted in 79 %, 70 %, and 76 % sensitivity, respectively, and 97 %, 96 %, and 94 % specificity, respectively [28]. Each question has four different options scored as 0, 1, 2, or 3. The scale rates the intensity of depressive symptoms over the previous 7 days. The total score ranges between 0 and 30. Having symptoms of depression was defined as having a total EPDS score ≥13 [27]. Validated translated versions of the original EPDS were available for eight languages other than English: Dutch, French, German, Icelandic, Norwegian, Slovenian, Spanish, and Swedish [29]. The Serbian version

was developed by two independent linguistic experts, who carried out translations and back-translations. Any discrepancies between the back-translated and original EPDS were identified and corrected. For the remaining five languages, the translated versions used in previous studies were utilised [30–33].

Statistical analysis
Descriptive statistics were used to calculate the prevalence of conventional and herbal medicines use against nausea during pregnancy and presented as percentages. Univariate and multivariate generalised estimating equation (GEE) analyses were performed to explore potential significant associations between the maternal characteristics listed in Table 1 and the use of conventional medicines against nausea. The GEE with the binary logistic model was used to correct for clustering on region of residency. Odds ratios (ORs) are presented with 95 % confidence intervals (CIs). All variables in Table 1, with the exception of multiple pregnancy, were included in the multivariate models.

Univariate and multivariate GEE analyses were also used to explore the relationships between co-morbidity and nausea and its treatment. First, univariate analyses were performed. Then full multivariate models were built including all variables presented in Table 1. Reduced models were fit by excluding non-significant variables (significance level: $p < 0.05$), unless removal of the variable caused a >10 % change in the effect estimates. Sub analyses including the EPDS were restricted to pregnant women only, as the EPDS is based on symptoms during the prior week. Moreover, stratified analyses on timing of gestation (during first trimester versus after first trimester) were performed when studying the association between nausea and comorbidity.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Statistics 20) for Windows (SPSS, Chicago, IL, USA).

Ethics
Before entering the online questionnaire, the respondents had to 1) read the study description in which the study objectives, the participants' right to withdraw at any time, and contact persons in the applicable country were presented, and 2) answer the following question: "Are you willing to participate in the study?" If the woman ticked "yes" as the answer it was considered informed consent.

The study was approved by the Regional Ethics Committee, Region South-East in Norway, and the relevant Ethics Boards in each specific country when required [23]. Complementary ethical approval was required and obtained from the Faculty of Medicine and Health Science Research Ethics Committee of the University of

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 4 of 13

Table 1 Factors related to nausea and treatment of nausea

	Total population	Total Nausea	Crude OR (95 % CI)	Adjusted OR (95 % CI)b	Nausea, conventional medicines against nausea	Crude OR (95 % CI)	Adjusted OR (95 % CI)b
	n = 9113 (% of 9113)	n = 6701 (% of total in row)	Nausea vs. no nausea	Nausea vs. no nausea	n = 1201 (% of total nausea in row)	Nausea, conventional medicines against nausea vs. Nausea, no treatmentc	Nausea, conventional medicines against nausea vs. Nausea, no treatmentc
Age, years							
≤24	1413 (15.5)	1053 (74.5)	1.1 (1.0-1.2)	1.2 (1.0-1.3)	183 (17.4)	0.9 (0.7-1.2)	0.9 (0.6-1.2)
25-29	3061 (33.6)	2236 (73.0)	1	1	417 (18.6)	1	1
30-34	2939 (32.3)	2191 (74.5)	1.1 (1.0-1.2)	1.0 (0.9-1.2)	399 (18.2)	1.0 (0.8-1.2)	1.0 (0.7-1.3)
≥35	1630 (17.9)	1162 (71.3)	0.9 (0.7-1.2)	0.8 (0.6-1.1)	185 (15.9)	0.8 (0.7-1.0)	0.9 (0.7-1.0)
Marital status							
Married/cohabiting	8578 (94.1)	6322 (73.7)	1	1	1137 (18.0)	1	1
Single/divorced/other	535 (5.9)	379 (70.8)	**0.9 (0.8-0.9)**	0.9 (0.9-1.0)	64 (16.9)	0.9 (0.8-1.1)	0.9 (0.6-1.2)
Parity							
0 previous live births	4602 (50.5)	3211 (69.8)	1	1	571 (17.8)	1	1
≥1 previous live births	4511 (49.5)	3490 (77.4)	**1.5 (1.4-1.6)**	**1.5 (1.3-1.7)**	630 (18.1)	1.0 (0.7-1.4)	1.0 (0.7-1.4)
Education							
Primary school	380 (4.2)	288 (75.8)	1.2 (0.9-1.6)	1.2 (0.8-1.8)	74 (25.7)	**1.6 (1.2-2.1)**	**1.5 (1.1-2.3)**
High school	2574 (28.2)	1901 (73.9)	1.0 (0.9-1.3)	1.1 (0.8-1.4)	309 (16.3)	0.9 (0.8-1.0)	0.9 (0.8-1.1)
University or college	5120 (56.2)	3738 (73.0)	1	1	657 (17.6)	1	1
Other education	1039 (11.4)	774 (74.5)	1.1 (1.0-1.2)	1.1 (0.9-1.3)	161 (20.8)	1.2 (1.0-1.6)	1.2 (1.0-1.6)
Working status							
Employed, but not as health care personnel	5417 (59.4)	3874 (71.5)	1	1	629 (16.2)	1	1
Health care personnel	1236 (13.6)	961 (77.8)	**1.4 (1.2-1.7)**	**1.3 (1.1-1.6)**	216 (22.5)	**1.4 (1.2-1.7)**	**1.4 (1.2-1.6)**
Unemployed	1991 (21.8)	1536 (77.1)	**1.3 (1.2-1.5)**	**1.3 (1.2-1.4)**	292 (19.0)	1.2 (1.0-1.3)	1.2 (1.0-1.5)
Other	457 (5.0)	323 (70.7)	1.0 (0.9-1.0)	0.9 (0.9-1.0)	62 (19.2)	1.2 (1.0-1.5)	1.1 (0.9-1.3)
Use of folic acid							
Before the pregnancy	311 (3.4)	237 (76.2)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	58 (24.5)	**1.5 (1.3-1.9)**	**1.6 (1.3-1.9)**
Before and during pregnancy	4077 (44.7)	3072 (75.3)	1	1	552 (18.0)	1	1
Only during pregnancy	3929 (43.1)	2821 (71.8)	0.8 (0.7-1.0)	**0.8 (0.7-1.0)**	488 (17.3)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
No	716 (7.9)	517 (72.2)	0.9 (0.7-1.1)	0.8 (0.7-1.1)	93 (18.0)	1.0 (0.6-1.7)	1.0 (0.6-1.7)

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 5 of 13

Table 1 Factors related to nausea and treatment of nausea *(Continued)*

Smoking during pregnancy							
No	8227 (90.3)	6125 (74.4)	1	1	1092 (17.8)	1	1
Yes	864 (9.5)	560 (64.8)	**0.6 (0.6-0.7)**	**0.6 (0.5-0.7)**	105 (18.8)	1.0 (0.8-1.3)	1.0 (0.8-1.3)
Pregnant population	n = 4938 (% of 4938)	n = 3762 (% of total in row)		**Adjusted OR (95 % CI)[d]**	n = 657 (% of total nausea in row)		**Adjusted OR (95 % CI)[d]**
Multiple pregnancy[a]							
No	4817 (97.5)	3667 (76.1)	1	1	636 (17.3)	1	1
Yes	76 (1.5)	65 (85.5)	1.9 (0.8-4.5)	2.0 (0.8-4.9)	17 (26.2)	**1.6 (1.1-2.3)**	**1.6 (1.1-2.4)**

Numbers do not add up due to missing numbers

Significant findings are in bold

Abbreviations: OR odds ratio; *CI* confidence interval

[a]This question was only posed to pregnant women (*n* = 4938). Only pregnant women are included in the analysis

[b]Adjusted for all other variables in the table with the exception of "multiple pregnancy"

[c]Nausea, no treatment includes women with nausea not using any of the following treatments against nausea: conventional medicines, herbal medicines, homeopathic medicines and dietary supplements

[d]Only pregnant women are included in the analysis. Variables included in the model: age, marital status, parity, education, working status, use of folic acid, and smoking

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 6 of 13

Table 2 Most common treatments against nausea by region and country

Region or country	Nausea	Use of any treatment[a]	Use of conventional medicines	Most frequently used conventional medicine	Use of herbal medicines	Most frequently used herbal medicine
	n (%)	n (%)	n (%)	(n)	n (%)	(n)
Western Europe (*n* = 3201)	2338 (73.0)	736 (23.0)	449 (14.0)	Antihistamines (174)	230 (7.2)	Ginger (203)
Austria (*n* = 82)	54 (65.9)	15 (18.3)	7 (8.5)	Antihistamines (3) and metoclopramide (3)	8 (9.8)	Ginger (8)
France (*n* = 374)	263 (70.3)	140 (37.4)	101 (27.0)	Metoclopramide (43)	7 (1.9)	Ginger (3)
Italy (*n* = 926)	645 (69.7)	193 (20.8)	77 (8.3)	Metoclopramide (25)	80 (8.6)	Ginger (71)
The Netherlands (*n* = 81)	58 (71.6)	14 (17.3)	12 (14.8)	Antihistamines (8)	3 (3.7)	Ginger (3)
Switzerland (*n* = 618)	436 (70.6)	213 (34.5)	165 (26.7)	Antihistamines (118)	49 (7.9)	Ginger (43)
United Kingdom (*n* = 1120)	882 (78.8)	161 (14.4)	87 (7.8)	Antihistamines (35)	83 (7.4)	Ginger (75)
Northern Europe (*n* = 2820)	2259 (80.1)	533 (18.9)	417 (14.8)	Antihistamines (316)	112 (4.0)	Ginger (107)
Finland (*n* = 574)	453 (78.9)	47 (8.2)	37 (6.4)	Metoclopramide (17)	3 (0.5)	Ginger (3)
Iceland (*n* = 71)	60 (84.5)	26 (36.6)	17 (23.9)	Antihistamines (12)	12 (16.9)	Ginger (11)
Norway (*n* = 1288)	1028 (79.8)	199 (15.5)	120 (9.3)	Antihistamines (74)	95 (7.4)	Ginger (92)
Sweden (*n* = 887)	718 (80.9)	261 (29.4)	243 (27.4)	Antihistamines (219)	2 (0.2)	Ginger (1) and black pepper (1)
Eastern Europe (*n* = 2342)	1512 (64.6)	303 (12.9)	146 (6.2)	Antacids (56)	121 (5.2)	Ginger (69)
Croatia (*n* = 286)	182 (63.6)	27 (9.4)	14 (4.9)	Antacids (5)	1 (0.3)	Other herbal products (1)
Poland (*n* = 679)	447 (65.8)	81 (11.9)	37 (5.4)	Antihistamines (16)	43 (6.3)	Ginger (36)
Russia (*n* = 1008)	625 (62.0)	146 (14.5)	81 (8.0)	Antacids (29)	59 (5.9)	Artichoke (28)
Serbia (*n* = 220)	144 (65.5)	29 (13.2)	13 (5.9)	Antacids (7)	0	-
Slovenia (*n* = 149)	114 (76.5)	20 (13.4)	1 (0.7)	Antacids (1)	18 (12.1)	Ginger (16)
North-America (*n* = 533)	415 (77.9)	171 (32.1)	137 (25.7)	Antihistamines (96)	46 (8.6)	Ginger (41)
Canada (*n* = 236)	177 (75.0)	85 (36.0)	74 (31.4)	Antihistamines (68)	19 (8.1)	Ginger (18)
USA (*n* = 297)	238 (80.1)	86 (29.0)	63 (21.2)	Ondansetron (29)	27 (9.1)	Ginger (23)
Australia (*n* = 217)	177 (81.6)	85 (39.2)	52 (24.0)	Metoclopramide (32)	47 (21.7)	Ginger (46)
Total population (*n* = 9113)	6701 (73.5)	1828 (20.1)	1201 (13.2)	Antihistamines (613)	556 (6.1)	Ginger (466)

[a]Including conventional medicines, herbal medicines, homeopathic medicines and dietary supplements
Antacids are defined as all medicines with ATC-code A02
Antihistamines are defined as all medicines with ATC-code R06

East Anglia in the UK, The National Bioethics Committee in Iceland and The Scientific Ethic Board, Provincial Health Service of Trento in Italy. The STROBE statements were used when writing this paper (Additional file 1).

Results

During the 2-month study period in each country, a total of 9113 women were included in the study. Respondents who were residents of Europe (Western, *n* = 3201; Northern, *n* = 2820; Eastern, *n* = 2342) constituted the largest proportion of the total study population, followed by North America (*n* = 533) and Australia (*n* = 217).

At the time of completing the questionnaire, 4938 (54.2 %) of the women were pregnant and 4175 (45.8 %) had given birth during the previous year. Among the pregnant respondents, 1067 (21.6 %), 1656 (33.5 %), and 2214 (44.8 %) were in the first, second, and third trimester of their pregnancy, respectively, and 182 (3.7 %) were less than 6 weeks pregnant. A total of 1913 (45.8 %) of the mothers had an infant less than 24 weeks of age.

Among the respondents, 6701 (73.5 %) had experienced nausea during pregnancy; 1828 (27.3 %) used some form of treatment against nausea and 4873 (72.7 %) did not. Conventional medicines against nausea were used by 1201 (17.9 %) of the women and herbal medicines by 556 (8.3 %).

Both the prevalence of nausea and its treatment varied by country and region (Table 2 and Fig. 1). The prevalence of nausea ranged from 62.0 % in Russia to 84.5 % in Iceland. The proportion of respondents treated among those who suffered from nausea ranged from 10.4 % in Finland to 53.2 % in France; the next highest proportions were in Switzerland (48.9 %), Canada (48.0 %),
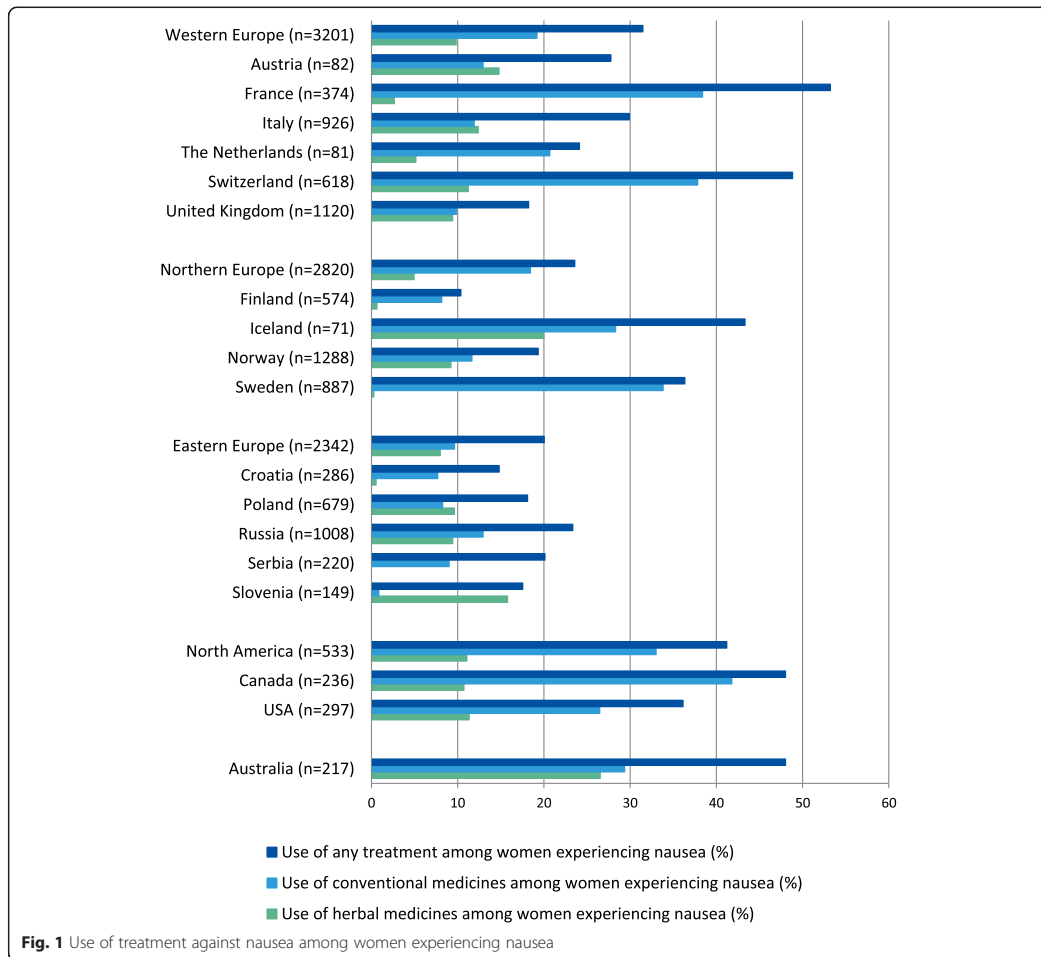
Fig. 1 Use of treatment against nausea among women experiencing nausea

and Australia (48.0 %). In 11 countries the treatment rates were below 30 % (Fig. 1). Among the regions, Australia (48.0 %) and North America (41.2 %) had the highest rates of treatment.

The most commonly used conventional medicines against nausea in the total population were antihistamines, which were used by 613 respondents (6.7 %) (Table 2 and Additional file 2). Metoclopramide was the second most commonly used medicine with 268 respondents (2.9 %). Antacids (ATC-group A02), ondansetron, and domperidone were used by 176 (2.6 %), 54 (0.6 %), and 48 (0.5 %) respondents, respectively. Conventional medicines were most commonly used against nausea in Canada, France, Switzerland and Sweden. The type of conventional

medicine most commonly used among women with nausea differed by region and country, but in the majority of countries it was either antihistamines or metoclopramide. An exception was ondansetron, which was the most commonly used medicine in the United States, closely followed by antihistamines. In Croatia, Russia, Serbia, and Slovenia the most common medicines were antacids, despite heartburn and reflux problems being less prevalent in these countries (60.5 %, 59.6 %, 52.7 %, and 57.7 %, respectively) compared to the total population (66.0 %). The countries in Eastern Europe had a low frequency of conventional medicines use. One respondent from Slovenia reported the use of conventional medicines. Interestingly, metopimazine was reported to be used against nausea by

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 8 of 13

29 respondents, all in France. In Canada, 54 respondents had used Diclectin®, which is a combination of the antihistamine doxylamine and pyridoxine.

Among the five regions, Australia had the highest frequency of herbal medicine use (21.7 %). Ginger was the most commonly used herbal medicine in the total population (5.1 %) and in most regions and countries. However, in Russia the most commonly used herbal medicine was artichoke (2.8 %). In most countries, herbal medicines were used to a lesser extent than conventional medicines, with the exception of Slovenia, Poland, Austria, and Italy.

Maternal characteristics as predictors of nausea and the use of conventional medicines against nausea during pregnancy are shown in Table 1. Respondents who had more than one previous live birth, worked as health care personnel, or were unemployed were more likely to experience nausea, whereas respondents who used folic acid during pregnancy only or smoked during pregnancy were less likely to experience nausea according to adjusted models. Respondents who had primary school as their highest completed education, were health care personnel, or had used folic acid before the pregnancy were more likely to have used conventional medicines against nausea than respondents with characteristics within the respective reference categories. Multiple pregnancy was also associated with use of medicines against nausea.

Women who experienced nausea during pregnancy were more likely to have any of the acute short-term illnesses listed in Table 3. These respondents were also more likely to have four or more co-morbidities in terms of acute short-term illnesses, any chronic illness, or to have taken sick leave during pregnancy. This pattern was similar when comparing respondents who had nausea and used conventional medicines against nausea to the respondents who experienced nausea without using any treatment. However, the effect estimates were generally lower than for nausea alone. Sub analyses including only respondents pregnant at the time of participation in the study revealed that respondents who experienced nausea were more likely to have symptoms of depression (EPDS score ≥13) than respondents without nausea. This was also true among respondents who had nausea and used conventional medicines compared to respondents who experienced nausea without treatment.

In an additional sub analysis we found that time of gestation acted as a plausible effect modifier of the association between medicated nausea and comorbidity. Specifically, respondents early in their pregnancy (≤1 trimester) who treated nausea with conventional medicines presented a significant 3.1-, 2.8-, and 2.1-fold increased likelihood of taking sick leave (crude OR: 3.1, 95 % CI: 1.8-5.5), having depressive symptoms during pregnancy (crude OR: 2.8, 95 % CI: 1.7-4.6), and having heartburn

and reflux problems (crude OR: 2.1, 95 % CI: 1.6-2.6), respectively, compared to respondents with non-medicated nausea. Such measures of association were of a much smaller magnitude (30-70 % increased likelihood) in the stratum comprising only respondents later in their pregnancy (>1 trimester). Similar results were observed when respondents with nausea were compared to those without nausea (data not shown).

Discussion

Variations were found across countries and regions in the prevalence of nausea, treatment rates, and types of treatment used against nausea during pregnancy. Cultural differences reflected in different treatment traditions, differences between countries with respect to the women's and general practitioners' willingness to treat, and variations in access to prenatal care and treatments and their relative costs may explain several of our findings. Among respondents suffering from nausea, less than one in three used any form of treatment, and only 18 % had used any medicine against this complaint. We do not have data on the severity of nausea, and the respondents may generally suffer from mild symptoms that are sufficiently managed by non-pharmacological treatments, such as dietary changes. However, the low prevalence of treatment may also be explained by a reluctance of many general practitioners to treat these women [34], or by an overestimation of the risk of medicines among pregnant women with nausea [35]. The overall prevalence of nausea (73.5 %) in this study is in accordance with a recent meta-analysis of NVP including 59 studies from various countries [1].

Canada, followed by France, Switzerland and Sweden, had the highest prevalence of conventional medicines use against nausea. This finding may be due to the clear and well known guidelines in this country [36, 37] and the antiemetic Diclectin®, which is approved for use against NVP. Therefore, simplifying the identification of safe and effective treatments may possibly increase the use of treatment. Among the European countries, medicine use was highest in France, which is in line with the results of a study of drug utilisation in pregnancy that included six European Registries of Congenital Anomalies in four European countries: France, Great Britain, Italy, and the Netherlands [38]. The authors of the study found that the two centres in France had the highest prevalence of medicine use (80.8 % and 74.2 %), and that antinauseants were the most frequently consumed drugs in this country (20.9 % and 15.0 %) [38]. We found that several French respondents used metopimazine, a dopamine antagonist, which was not reported in any of the other countries. This finding is in accordance with a comparative study by Einarson and colleagues in 1998 in which France was the only country to list metopimazine as a treatment option [14].

Heitmann et al. BMC Pregnancy and Childbirth (2015) 15:321

Page 9 of 13

Table 3 Co-morbidities according to nausea in pregnancy and its treatment

	Total population	Nausea	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Nausea, conventional medicines against nausea	Crude OR (95 % CI)	Adjusted OR (95 % CI)
	n = 9113 (% of 9113)	n = 6701 (% of 6701)	Nausea vs. No nausea	Nausea vs. No nausea	n = 1201 (% of 1201)	Nausea, conventional medicines against nausea vs. Nausea, no treatment[a]	Nausea, conventional medicines against nausea vs. Nausea, no treatment[a]
Heartburn or reflux problems	6011 (66.0)	4703 (70.2)	2.0 (1.8-2.1)	2.0 (1.8-2.1)[e]	908 (75.6)	1.4 (1.2-1.7)	1.4 (1.1-1.7)[f]
Sleeping problems	5207 (57.1)	4107 (61.3)	1.9 (1.7-2.1)	1.9 (1.8-2.1)[e]	798 (66.4)	1.3 (1.2-1.5)	1.3 (1.2-1.5)[f]
Constipation	4757 (52.2)	3686 (55.0)	1.5 (1.4-1.7)	1.5 (1.3-1.7)[e]	678 (56.5)	1.1 (0.9-1.3)	1.1 (0.9-1.3)[f]
Headache	5014 (55.0)	3983 (59.4)	2.0 (1.9-2.0)	1.9 (1.8-2.0)[e]	767 (63.9)	1.3 (1.2-1.3)	1.3 (1.2-1.4)[f]
Pain in neck, back or pelvic girdle	6227 (68.3)	4798 (71.6)	1.7 (1.5-2.0)	1.7 (1.5-1.9)[e]	910 (75.8)	1.3 (1.1-1.5)	1.3 (1.1-1.6)[f]
Any chronic illness[b]	2273 (24.9)	1738 (25.9)	1.2 (1.2-1.3)	1.2 (1.2-1.3)[e]	361 (30.1)	1.2 (1.2-1.3)	1.3 (1.0-1.6)[f]
≥4 co-morbidities[c]	5257 (57.7)	4245 (63.3)	2.4 (2.2-2.6)	2.3 (2.2-2.5)[e]	849 (70.7)	1.5 (1.3-1.8)	1.5 (1.3-1.8)[f]
Sick leave during pregnancy	3956 (43.4)	3001 (44.8)	1.2 (1.0-1.5)	1.3 (1.1-1.6)[e]	625 (52.0)	1.4 (1.1-2.0)	1.5 (1.1-2.2)[f]
Pregnant population	n = 4938 (% of 4938)	n = 3762 (% of 3762)	Crude OR (95 % CI)	Adjusted OR (95 % CI)	n = 657 (% of 657)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Symptoms of depression during pregnancy[d]	863 (17.5)	718 (19.1)	1.7 (1.6-1.8)	1.5 (1.4-1.6)[g]	183 (27.9)	1.9 (1.5-2.3)	1.9 (1.5-2.4)[h]

Abbreviations: OR odds ratio; *CI* confidence interval
Significant findings are in bold
[a]Nausea, no treatment: Includes women with nausea not using any of the following treatments against nausea: conventional medicines, herbal medicines, homeopathic medicines and dietary supplements.
[b]Any chronic illness includes asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular diseases, and other
[c]≥ 4 co-morbidities includes women who reported experiencing more than three of the following disorders during pregnancy: heartburn or reflux problems, constipation, common cold, urinary tract infections, other infections, pain in the neck, back, or pelvic girdle, headache, and sleeping problems.
[d]Only women who were pregnant at the time of participating are included (n = 4938). Symptoms of depression were measured by the Edinburgh Postnatal Depression Scale. Symptoms of depression were defined as an EPDS score of ≥ 13
[e]Adjusted for age, parity, working status, use of folic acid, and smoking during pregnancy
[f]Adjusted for age, education, working status, and use of folic acid
[g]Adjusted for age, parity, working status, smoking during pregnancy, and ≥4 co-morbidities
[h]Adjusted for education, working status, use of folic acid, multiple pregnancy, and ≥4 co-morbidities

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 10 of 13

In Sweden, antihistamines were the most frequently used medicines against nausea, which is also in line with previous findings [17].

Antihistamines and metoclopramide were the most commonly used conventional medicines against nausea in the vast majority of the countries. The exceptions were the USA, Croatia, Russia, Serbia, and Slovenia, where ondansetron (USA) and antacids (Croatia, Russia, Serbia, and Slovenia) were the most commonly used medicines against nausea. This is in line with findings of a study of hyperemesis gravidarum treatments detecting inter-country variations of frequency of different treatments of which serotonin inhibitors were most frequently used in the USA, antihistamines in Canada, whereas Australia had the highest reported use of pro-motility agents such as metoclopramide [39]. Meta-analyses and epidemiological studies have not found a higher risk of malformations with antihistamines and metoclopramide [40–43], and antihistamines are regarded as a first line treatment according to guidelines in both North America and Europe [36, 37, 44–46]. Recently, the safety of metoclopramide and ondansetron has been questioned [47, 48]. In July 2013, the European Medicines Agency (EMA) recommended changing the use of metoclopramide to 10 mg three times a day up to 5 days to reduce the risk of extrapyramidal side effects [48]. As this is seldom long enough to treat NVP, the change will limit this medicine's usefulness for nausea and vomiting in the pregnant population. In 2011, the U.S. Food and Drug Administration (FDA) raised concerns over cardiovascular safety, suggesting that ondansetron could cause prolonged QT interval, which can lead to Torsade de Pointes [49]. Electrocardiogram (ECG) monitoring in patients with electrolyte abnormalities is advised. A recent Danish registry study of ondansetron use during the first trimester did not detect any increased risk of malformations [50]. Another unpublished study based on the same registries detected a 2-fold increase in the prevalence of major congenital heart defects after exposure to ondansetron [51]. Notably, the data in our study were collected during winter 2011–2012. Therefore, the medication utilisation pattern may have changed due to the warnings issued by the EMA (2013) and FDA (2011) with respect to metoclopramide and ondansetron, respectively.

Australia had the highest rate of herbal medicine use against nausea, followed by Iceland and Slovenia. Australia has previously been reported to have a high prevalence of herbal medicine and CAM use in pregnancy in general [52, 53], and also more specifically a high use of ginger during pregnancy [52]. The results with respect to Slovenia were special; 12.1 % of respondents had used herbal medicine, but only one respondent had used a conventional medicine against nausea. This finding may indicate a long tradition of herbal medicine in Slovenia or a lack of access to conventional medicines.

Ginger was the dominant herbal medicine used against nausea. Ginger has been reported to be more effective than placebo and equally effective as vitamin B6 and dimenhydrinate against nausea in pregnancy [54]. With respect to safety, a cohort study with 1020 ginger-exposed pregnancies (466 in the first trimester) found no increased risk of malformations, stillbirth/perinatal death, low birth weight, preterm birth, or low Apgar score [16]. Russia was the only country to report the use of artichoke against nausea. However, no studies of artichoke use in pregnancy were found, though artichoke has been observed to have an antiemetic effect in outpatients with dyspeptic syndrome [55].

Various maternal characteristics were associated with nausea and its treatment. Having more than one previous live birth was associated with nausea, probably because having additional children results in less time to rest and relieve the nausea. This finding is in accordance with previous research [56, 57], but the data are conflicting [4]. Other factors associated with nausea were working as health care personnel or being unemployed, which is in line with previous research that found an association between being a housewife or out of work and nausea [57, 58]. Respondents who smoked during pregnancy or who used folic acid during pregnancy were less likely to report nausea. Decreased risk of nausea among smokers was observed in several earlier studies [4, 56, 57]. Use of vitamins in early pregnancy was previously found to be protective against nausea [57, 59]. Women who take folic acid before, as well as during, pregnancy are most likely planning to become pregnant, and this may imply that they are more attentive to early symptoms of pregnancy than women who use folic acid only during pregnancy.

Respondents who had a lower education were more likely to use medicines against nausea. This finding is in accordance with a Swedish study [17]. Respondents working as health care professionals were also more likely to use medicines against nausea, which can be explained by this group being aware of safe and effective treatment options for nausea. Multiple pregnancy was associated with the use of medicines. This may indicate that use of medicines may act as a marker of severe forms of nausea, as it is previously found that multiple pregnancy increase the risk of nausea [56]. In addition, the severity of NVP symptoms has been associated with the use of antiemetics [7, 60].

We found a high burden of co-morbidity among respondents experiencing nausea during pregnancy. The association with symptoms of depression and sick leave in particular warrants attention. Women who suffer from any pregnancy-related complaint may tend to seek information on the internet to a greater extent than women who feel

well. Therefore, the respondents may be seeking information and responding at the peak of their discomfort. However, symptoms of depression have also been associated with nausea during pregnancy [7, 9, 60]. Similarly, the association with heartburn and reflux problems is in agreement with previous studies [61]. Clinicians should be aware of the high degree of co-morbidity with nausea and routinely ask women with nausea whether they have reflux problems or other pregnancy-related ailments.

Our findings indicate that women who have nausea in early pregnancy, especially those who treat nausea with medicines, have a high likelihood of experiencing depressive symptoms, heartburn and reflux problems, and taking sick leave. This is an important clinical finding and emphasises how debilitating nausea during pregnancy can be for these women. General practitioners in contact with women with NVP should be aware of the high degree of co-morbidity, examine these women for symptoms of depression and heartburn and reflux problems, and treat these conditions if present. Special attention should be paid to women in early pregnancy. Treating heartburn and reflux problems may alleviate symptoms of NVP and increase the women's wellbeing [62]. Major guidelines suggest antacids as adjunctive therapy against NVP [36, 37, 44].

This study has several strengths and limitations that should be acknowledged. This is the first multinational study to simultaneously collect data on the prevalence of nausea and its treatment, which enables direct comparisons between countries and regions. A large number of women from a variety of countries in different regions of the world were reached due to the utilisation of a web-based questionnaire posted on various pregnancy-related websites. These data provide valuable insights into the prevalence of nausea and the treatment of this complaint across countries and regions. Furthermore, the study population was reasonably comparable to the general birthing population with respect to age, parity, and smoking habits, though the women in the study population had a higher education on average [23]. However, the possibility that the respondents differ from the general birthing population in ways that our analysis cannot control for cannot be excluded. In some of the countries (Australia, Canada, France, Russia, the Netherlands, and the USA), the study sample was a small proportion of the general birthing population. For these specific countries, our findings should be generalised with caution.

There are some other limitations that need to be addressed. First, a conventional response rate could not be calculated because the questionnaire was only accessible through websites. However, epidemiological studies have indicated that web-based recruitment methods have reasonable validity [63, 64]. In addition, women of childbearing age generally have a relatively high internet penetration

rate [65–67]. The fact that we found a prevalence of nausea very similar to the prevalence reported in the literature, and that the comparison with the birthing population in each participating country had high external validity, supports our approach. However, the higher education of the respondents may have had an impact on their choice of treatment. Second, including women at an early stage in their pregnancy may underestimate the prevalence of nausea, as this complaint often does not occur before gestational weeks 6–8. However, this only applies to the 182 women (2.0 %) who were less than 6 weeks pregnant at the time of participation. Thirdly, although we tried to minimise the risk of recall bias by excluding women with a youngest child aged >1 year, this risk cannot be ruled out. In addition, the EPDS was only measured at one time point during the pregnancy and two time points are considered more valid [29]. Finally, we lack information on the severity of nausea and our results should be interpreted with these limitations in mind.

Conclusions

The prevalence of nausea was high across all participating countries, but its treatment varied, possibly due to cultural differences and differences in attitudes towards medicines. Women who reported nausea also had a high burden of co-morbidity, especially heartburn and reflux symptoms. The association with symptoms of depression and sick leave warrants attention. These findings will be helpful to health care personnel involved in the care of pregnant women with nausea.

Additional files

> **Additional file 1: STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies.* (PDF 96 kb)**
>
> **Additional file 2: Most common medicines used against nausea on 1st and 2nd ATC level according to timing of use in pregnancy among women with nausea in pregnancy.** Description of data: A table containing the most common medicines on the 1st and 2nd ATC levels used against nausea according to the timing of use in pregnancy among women with nausea. (PDF 21 kb)

Abbreviations used

NVP: Nausea and vomiting during pregnancy; CAM: Complementary and alternative medicine; OTC medicine: Over-the-counter medicine; ATC: Anatomical Therapeutic Chemical; WHO: World Health Organization; EPDS: Edinburgh Postnatal Depression Scale; GEE analyses: Generalised estimating equation analyses; OR: Odds ratio; CI: Confidence interval; SPSS: Statistical Package for the Social Sciences; EMA: the European Medicines Agency; FDA: the U.S. Food and Drug Administration; ECG: Electrocardiogram.

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 12 of 13

References

1. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol. 2013; 20:e171–183.
2. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43:245–8.
3. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182:931–7.
4. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol. 1985;66:612–6.
5. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol. 2000;40:397–401.
6. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186:S220–227.
7. Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol. 2000;21:129–36.
8. O'Brien B, Evans M, White-McDonald E. Isolation from "being alive": coping with severe nausea and vomiting of pregnancy. Nurs Res. 2002;51:302–8.
9. Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. J Nurs Scholarsh. 2003;35:119–25.
10. Dorheim S, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. BJOG. 2013;120(5):521–30.
11. Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. Curr Med Res Opin. 2007;23:833–40.
12. Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. J Popul Ther Clin Pharmacol. 2013;20:e149–160.
13. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66:207–14.
14. Einarson A, Koren G, Bergman U. Nausea and vomiting in pregnancy: a comparative European study. Eur J Obstet Gynecol Reprod Biol. 1998;76:1–3.
15. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? BJOG. 2008;115:1484–93.
16. Heitmann K, Nordeng H, Holst L. Safety of ginger use in pregnancy: results from a large population-based cohort study. Eur J Clin Pharmacol. 2013;69: 269–77.
17. Asker C, Norstedt Wikner B, Kallen B. Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol. 2005;61:899–906.
18. Hollyer T, Boon H, Georgousis A, Smith M, Einarson A. The use of CAM by women suffering from nausea and vomiting during pregnancy. BMC Complement Altern Med. 2002;2:5.
19. Chandra K, Magee L, Einarson A, Koren G. Nausea and vomiting in pregnancy: results of a survey that identified interventions used by women to alleviate their symptoms. J Psychosom Obstet Gynaecol. 2003;24:71–5.
20. Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res A Clin Mol Teratol. 2012; 94:22–30.
21. van Gelder M, Pijpe A. E-epidemiology: a comprehensive update. Cancer. 2013;15:0.007.
22. Huybrechts KF, Mikkelsen EM, Christensen T, Riis AH, Hatch EE, Wise LA, et al. A successful implementation of e-epidemiology: the Danish pregnancy planning study 'Snart-Gravid'. Eur J Epidemiol. 2010;25:297–304.
23. Lupattelli A, Spigset O, Twigg M, Zagorodnikova K, Mårdby A, Moretti M, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ open. 2014;4:e004365.
24. Martindale W, Sweetman SC. Martindale: the complete drug reference. London: Pharmaceutical Press; 2011.
25. WHO Collaborating Centre for Drugs Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. http://www.whocc.no/atc_ddd_index/. Accessed 19 March 2015.
26. Kennedy DA, Lupattelli A, Koren G, Nordeng H. Herbal medicine use in pregnancy: results of a multinational study. BMC Complement Altern Med. 2013;13:355.
27. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782–6.
28. Bergink V, Kooistra L, den Berg MP L-v, Wijnen H, Bunevicius R, van Baar A, et al. Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res. 2011;70:385–9.
29. Cox JL, Holden J. Perinatal mental health: a guide to the Edinburgh Postnatal Depression Scale (EPDS). RCPsych Publications;2003.
30. Department of Health. Edinburgh Postnatal Depression Scale (EPDS): Translated versions – validated. Perth, Western Australia: State Perinatal Mental Health Reference Group. Government of Western Australia; 2006.
31. Grote V, Vik T, von Kries R, Luque V, Socha J, Verduci E, et al. Maternal postnatal depression and child growth: a European cohort study. BMC pediatrics. 2010;10:14.

Heitmann *et al. BMC Pregnancy and Childbirth* (2015) 15:321

Page 13 of 13

32. Stewart DE, Gagnon A, Saucier JF, Wahoush O, Dougherty G. Postpartum depression symptoms in newcomers. Can J Psychiatry. 2008;53:121–4.
33. Tamminen T. Postnatal depression, breastfeeding and mother-infant interaction. Unpublished doctoral thesis. Tampere, Finland: University of Tampere; 1990.
34. Gadsby R, Barnie-Adshead T, Sykes C. Why won't doctors prescribe antiemetics in pregnancy? BMJ. 2011;343:d4387.
35. Mazzotta P, Magee LA, Maltepe C, Lifshitz A, Navioz Y, Koren G. The perception of teratogenic risk by women with nausea and vomiting of pregnancy. Reprod Toxicol. 1999;13:313–9.
36. Maltepe C, Koren G. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum–a 2013 update. J Popul Ther Clin Pharmacol. 2013;20:e184–192.
37. Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24:817–31. quiz 832–813.
38. De Vigan C, De Walle HEK, Cordier S, Goujard J, Knill-Jones R, Ayme S, et al. Therapeutic drug use during pregnancy: A comparison in four European countries. J Clin Epidemiol. 1999;52:977–82.
39. Goodwin TM, Poursharif B, Korst LM, MacGibbon KW, Romero R, Fejzo MS. Secular trends in the treatment of hyperemesis gravidarum. Am J Perinatol. 2008;25(3):141–7.
40. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol. 1997;14:119–24.
41. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neona. 2002;11:146–52.
42. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Melbye M, Hviid A. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. JAMA. 2013;310:1601–11.
43. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. New Engl J Med. 2009;360:2528–35.
44. Smith J, Refuerzo J, Ramin S. Treatment and outcome of nausea and vomiting of pregnancy. UpToDate. 2014.
45. National Collaborating Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman. http://www.nice.org.uk/guidance/cg62/resources/guidance-antenatal-care-pdf. Accessed 19 March 2015.
46. ACOG (American College of Obstetrics and Gynecology) Practice Bulletin No. 153: Nausea and vomiting of pregnancy. Obstet Gynecol. 2015; 126(3):e12-24.
47. Koren G. Scary Science: Ondansetron Safety in Pregnancy-Two Opposing Results From the Same Danish Registry. Therapeutic drug monitoring 2014. [Epub ahead of print].
48. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146500.pdf. Accessed 19 March 2015.
49. FDA. Drug safety communication: Abnormal heart rythms may be associated with use of Zofran (ondansetron). http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm. Accessed 19 March 2015.
50. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. The New England journal of medicine. 2013;368: 814–23.
51. Andersen JT, Jimenez-Solem E, Andersen NL, Poulsen HE. Ondansetron use in early pregnancy and the risk of congenital malformations-a register based nationwide cohort study. Pharmacoepidemiol Drug Saf. 2013;22:13–4.
52. Forster DA, Denning A, Wills G, Bolger M, McCarthy E. Herbal medicine use during pregnancy in a group of Australian women. BMC Pregnancy Childbirth. 2006;6:21.
53. Frawley J, Adams J, Sibbritt D, Steel A, Broom A, Gallois C. Prevalence and determinants of complementary and alternative medicine use during pregnancy: results from a nationally representative sample of Australian pregnant women. Aust N Z J Obstet Gynaecol. 2013;53:347–52.
54. Dante G, Pedrielli G, Annessi E, Facchinetti F. Herb remedies during pregnancy: a systematic review of controlled clinical trials. J Matern Fetal Neonatal Med. 2013;26:306–12.
55. Kraft K. Artichoke leaf extract - Recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts. Phytomedicine. 1997;4:369–78.
56. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol. 2006;20:270–8.

57. Kallen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. Acta obstetricia et gynecologica Scandinavica. 2003;82:916–20.
58. Weigel MM, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. Am J Epidemiol. 1988;127:562–70.
59. Emelianova S, Mazzotta P, Einarson A, Koren G. Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. Clinical and investigative medicine Medecine clinique et experimentale. 1999;22:106–10.
60. Kramer J, Bowen A, Stewart N, Muhajarine N. Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. MCN Am J Matern Child Nurs. 2013;38:21–7.
61. Gill SK, Maltepe C, Koren G. The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy. Can J Gastroenterol. 2009; 23:270.
62. Gill SK, Maltepe C, Mastali K, Koren G. The effect of Acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. Obstet Gynecol Int. 2009;2009:585269.
63. Ekman A, Dickman PW, Klint A, Weiderpass E, Litton JE. Feasibility of using web-based questionnaires in large population-based epidemiological studies. Eur J Epidemiol. 2006;21:103–11.
64. van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? Am J Epidemiol. 2010;172:1292–8.
65. Seybert H. Internet use in households and by individuals in 2011. http://ec. europa.eu/eurostat/documents/3433488/5579964/KS-SF-11-066-EN.PDF/090e071f-c3a9-45d8-aa90-9b142251fd3a?version=1.0. Accessed 19 March 2015.
66. Internet World Stats. Usage and population statistics. 2012. Available from: http://www.internetworldstats.com/. Accessed 19 March 2015.
67. United States Census Bureau. The 2012 Statistical Abstract. Information & Communications; 2010. Available from: http://www.census.gov/compendia/statab/cats/information_communications/internet_publishipu_and_broadcasting_and_internet_usage.html. Accessed 19 March 2015.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1 **p1,3**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 **p4,5**	Explain the scientific background and rationale for the investigation being reported
Objectives	3 **p5**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 **p5,6**	Present key elements of study design early in the paper
Setting	5 **P5,6**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 **p6**	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 **p6,7,8**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* **p6,7,8**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 **p6,7,9, 18,19**	Describe any efforts to address potential sources of bias
Study size	10 **P5,6,10**	Explain how the study size was arrived at
Quantitative variables	11 **p6,7,8**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 **p9**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **p6 + ref. #23**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **p10,12 table 1**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest

Outcome data	15* **p11,12 + tables**	Report numbers of outcome events or summary measures
Main results	16 **p11,12 + tables**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 **p13**	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 **p13,14**	Summarise key results with reference to study objectives
Limitations	19 **p18,19**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **p14-19**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **p18,19**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **p20,22**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Additional file 1: Most common medicines used against nausea on 1st and 2nd ATC level according to timing of use in pregnancy among women with nausea in pregnancy (n=6701)*

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels	Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
A **Alimentary tract and metabolism**	**564 (8.4)**	**448 (6.7)**	**249 (3.7)**	**141 (2.1)**
A02 Drugs for acid related disorders	176 (2.6)	105 (1.6)	83 (1.2)	78 (1.2)
A03 *Drugs for functional gastrointestinal disorders*	316 (4.7)	277 (4.1)	137 (2.0)	52 (0.8)
A04 Antiemetics and antinauseants	90 (1.3)	81 (1.2)	47 (0.7)	22 (0.3)
A05 Bile and liver therapy	12 (0.2)	9 (0.1)	6 (0.1)	1 (0.0)
A07 Antidiarrheals, intestinal antiinflammatory/antiinfective agents	17 (0.3)	13 (0.2)	5 (0.1)	2 (0.0)
N **Nervous system**	**115 (1.7)**	**81 (1.2)**	**74 (1.1)**	**34 (0.5)**
N02 *Analgesics*	83 (1.2)	54 (0.8)	52 (0.8)	24 (0.4)
N05 Psycholeptics	32 (0.5)	27 (0.4)	22 (0.3)	10 (0.2)
R **Respiratory system**	**620 (9.3)**	**536 (8.0)**	**319 (4.8)**	**111 (1.7)**
R06 *Antihistamines for systemic use*	613 (9.2)	533 (8.0)	316 (4.7)	108 (1.6)
- Unspecified	82 (1.2)	57 (0.9)	46 (0.7)	17 (0.3)
Total medicine use (any ATC)	**1201 (17.9)[a]**	**965 (14.4)**	**577 (8.6)**	**254 (3.8)**
Total vitamin and/or mineral use (*ATC-class: A11-13, B03 and Unspecified supplement*)	**106 (1.6)**	**90 (1.3)**	**42 (0.6)**	**9 (0.1)**

*Only medicine groups used by more than 10 women are presented. Exposure timing is defined as follows: 1st trimester (gestational weeks 0-12), 2nd trimester (gestational week 13-24), 3rd trimester (gestational week 25 and up to childbirth).

[a] Numbers do not add up to total due to some women may have used more than one medicine

PAPER III

III

Nausea in pregnancy - attitudes among pregnant women and general practitioners on treatment and pregnancy care

Kristine Heitmann, MScPharm[1], Hans Christian Svendsen, MScPharm[2], Ingvild H. Sporsheim, MScPharm[3], Lone Holst, PhD[1]

[1]University of Bergen; Department of global public health and primary care; Post Box 7804, N-5018 Bergen, Norway; kristine.heitmann@igs.uib.no

[2] Apotek 1, Galleriet, Bergen, Norway

[3] The Hospital Pharmacy in Trondheim, Trondheim, Norway

Corresponding author: Kristine Heitmann, University of Bergen; Department of global public health and primary care; Post Box 7804, N-5018 Bergen; e-post address kristine.heitmann@igs.uib.no; telephone number +47 55586006, fax number +47 55586130

Word count (excluding key points, abstract, table, reference list, acknowledgements): 4917

Short running title: Nausea in pregnancy and pregnancy care

Key points:

Nausea and vomiting during pregnancy (NVP) is very common, and of clinical significance for 35% of the women.

- While the GPs agreed on the importance of normalising the symptoms, the women felt their distress was trivialised, and missed being properly evaluated.

- Both the GPs and the women showed a reluctant attitude to medical treatment of NVP.

- The GPs gave the impression of only considering medical treatment after progression of symptoms to become quite severe.

Abstract

Objective: Nausea and vomiting during pregnancy (NVP) is very common, and may have great impact on a woman's life. The aim of this study was to explore thoughts and attitudes among Norwegian pregnant women and GPs on treatment of NVP and pregnancy care.

Design: Focus group study.

Setting and subjects: Separate focus group discussions were conducted with pregnant women and GPs.

Results: Two focus group discussions were conducted with pregnant women and two with GPs. The GPs thought it was important to normalise NVP symptoms. However, the women felt their distress due to NVP was trivialised by the GPs. The women were sceptical towards medicines use while pregnant, and avoidance was sought despite being ill. The GPs appeared uncertain with respect to medical treatment of NVP, which was expressed to only be considered after progression to quite severe symptoms. Sick leave seemed to be an important part of the treatment regime applied by the GPs. The women had good experiences with graded sick leave.

*Conclusion***:** This Norwegian study identifies attitudes among GPs and pregnant women that may act as obstacles to appropriate care for women with NVP. The pregnant women and the GPs seemed to talk at cross purposes; GPs normalisation of the symptoms made the women feel their distress due to NVP was trivialised by the GPs. Our results indicate that pregnant women with NVP requiring medical treatment probably need comprehensive reassurance of no evidence of risk, before considering using any medicines.

Key words: nausea, vomiting, pregnancy, therapeutics, general practice

Background

Nausea affects around 70% of pregnant women [1]. Approximately 50% experience additional vomiting [2, 3]. Symptoms typically initiate during pregnancy week 6-8, peaking around week 11-13 and subside within week 16 [2, 3]. The prevalence of hyperemesis gravidarum (HG), the most severe form of nausea during pregnancy, is about 1% [4]. HG is characterised by dehydration and electrolyte imbalance, and often leads to hospitalisation [5].

Though some women privately celebrate the symptoms of nausea as one of the first signs of a longed-for pregnancy [6], prolonged nausea and vomiting during pregnancy (NVP) can be very debilitating for the women. For about 35% of the women, NVP is clinically significant [2, 5]. NVP severely reduces the women's quality of life, and feelings of isolation and helplessness are reported [7-9]. The ability to carry out daily activities is impaired, including parenting, partly due to less interaction with their children [9]. Women report that NVP adversely affects social functioning, relationship with partner, and also their partner's daily life [9, 10]. Additionally, it leads to consumption of resources in the health care system, and increased socio-economic costs with increasing severity of NVP [11, 12]. NVP is one of the main reasons for being on sick leave during pregnancy, reported to be responsible for almost one third of total sick leave during pregnancy [13]. In Norway, as an employee, you are entitled to sickness benefits if you are occupationally disabled due to own illness or injury and fulfil the demands to an employee as set by The Norwegian Labour and Welfare Administration (Norwegian short name: NAV) [14]. Sick leave certificates can be issued by physicians. You get sickness benefits equivalent to full wages (up to a set amount), paid by your employer the first 16 calendar days, and then by NAV [14]. The sick leave may be full time or graded (partial). The pregnancy care program in Norway is

free of charge and pregnant women are entitled to nine routine consultations with either their GP or a midwife, and additional consultations if required [15].

General practitioners (GPs) in the UK are alleged to be reluctant to the use of treatment against NVP [16]. Given that NVP is one of the most commonly experienced pregnancy complaints, and most often self-limiting, women presenting with NVP may not always be taken seriously. Canadian and American guidelines recommend early treatment of the symptoms of NVP to reduce costs related to hospitalisations, contacts with pregnancy care units, and sick leave, arguing that early symptoms are easier to treat [17, 18]. Given that NVP is most commonly experienced during the first trimester, and consequently during organogenesis, many women and prescribers may be reluctant to the use of medications to treat this complaint. This is reflected in a study from the USA reporting that only 15% of women suffering from NVP used any pharmacologic treatment [19]. Insufficient safety data, preference for non-pharmacologic methods and being made to feel uncomfortable by the physician are reported as common reasons for not using medicines against NVP among Canadian women [20]. It is well known that pregnant women often overestimate the risk of medications during pregnancy [21, 22]. Various Norwegian treatment guidelines for NVP exist [23-26], but no medicines have NVP as an approved indication in Norway, which further complicates the picture.

The aim of this study was to explore the thoughts and attitudes among Norwegian pregnant women and GPs on treatment of NVP and pregnancy care.

Design, material and methods

A focus group study was conducted with two groups of pregnant women during November - December 2012 and two groups of GPs during December 2013. Women attending routine

ultrasound examination in pregnancy week 17-18, and who had experienced NVP in current pregnancy, received an information brochure together with an invitation to the study. Snowball recruitment was also used as a strategy due to slow response among pregnant women at the antenatal clinic. At time of participation, all women were still pregnant. In total, 10 women were recruited and distributed in two focus groups of four and six participants, respectively (Table 1). The discussions lasted approximately 60 minutes. The women were asked to tell about their own thoughts on and experiences with pregnancy care and treatment of NVP.

To recruit GPs, educational groups for authorised and practicing GPs under specialisation in general practice were contacted via e-mail. Slow recruitment was also experienced with respect to this source population. Two focus group discussions were conducted, each lasting 60 minutes, with five GPs in each group (Table 1). The GPs were asked to talk about their experience with and thoughts on treatment of NVP.

All focus group discussions were conducted according to an interview guide to facilitate open discussion on pre-identified themes [27]. Separate interview guides were developed specifically for the pregnant women and the GPs. However, divergences from the interview guides occurred to facilitate a natural conversation in the group. Three of the authors acted as group moderators (HCS, IHS, LH), and one co-moderator in each group took field notes. The focus group discussions were audio-recorded and transcribed verbatim. The transcripts from the focus group discussions with the GPs and the pregnant women were analysed separately, according to the principles of systematic text condensation as described by Malterud [28]. Firstly, the transcripts were read as a whole by three of the authors to establish an overview of data, followed by the identification of preliminary themes representing different aspects of the participants' thoughts on and attitudes to treatment of NVP. Collaborative negotiation strategy was applied. Secondly,

meaning units (a text fragment that contains information about the research question) were sorted under the appropriate themes or code groups. Thirdly, the content of the coded groups was reduced into a condensate aiming to capture the essence of the meaning units. Lastly, descriptions and concepts were developed based on the condensates.

The study was approved by the Regional Committee for Ethics in Medical Research, Region West, and the Norwegian Data Inspectorate.

Results

The pregnant women

A call for acknowledgement

The women felt that their NVP was trivialised by their GP. Even after it was emphasised that NVP strongly impaired daily life functioning and general wellbeing, the women were told that symptoms of nausea are completely normal and expected as part of being pregnant. The women felt they weren't taken seriously, and missed acceptance and acknowledgement from their GP of how debilitating NVP is to live with. Impact on social life and work situation was mentioned. One woman also said it was hard not being fully able to care for her other children who were too young to understand why their mother couldn't play with them.

> "I told my GP that I was very bothered with nausea. However, he just responded that nausea is very normal, and that all pregnant women had it just like me. Nothing to worry about. Even when I tried to emphasise on the huge impact the nausea had on my daily life, I just got the impression that it was as expected." (W5)

Furthermore, they missed being evaluated properly for the severity of their symptoms, and wanted to be asked about their general well-being, weight and diet. A close follow-up was a request from many of the participants.

Inconsistent information resulted in scepticism and insecurity

Information on treatment of NVP was sought from numerous sources; GPs, pharmacies, internet, family and friends. Family, especially mothers, was a good source of advice on folk remedies. However, the women experienced a generational gap, themselves being more sceptical to folk remedies than their mothers or grandmothers. Though advice from pregnancy fora on the internet was taken with a pinch of salt, it could be used as an idea bank. Health care personnel were considered the most trustworthy source of information, and medical advice anchored in evidence-based medicine was expected. However, the experience of many of the participants was that information on treatment was inconsistent between different health care personnel, which made the participants feel frustrated, scared and insecure.

> "You shouldn't be given many different answers [from various healthcare personnel].
> You are sceptical and insecure to begin with thinking that you are carrying something in
> your belly that you may harm. If you ask around for advice and get many different
> answers, this is very frustrating and annoying." (W1)

Feelings of guilt

A healthy life style, including a healthy diet and regular exercise, was recognised by the participants as important during pregnancy. However, a strict focus on this by health care

personnel while the women were suffering from NVP, made the participants feel guilty due to not being able to fulfil these expectations. When they felt sick, they had to eat or drink whatever they could handle, even if this meant less healthy types of food and drinks, like crisps and soft drinks.

> "One might say that focus on a healthy diet is important, but I think most pregnant women know what you should or should not eat. In this condition it is all about what I actually am able to eat. It would feel good to be met by health care personnel that understand this."
> (W6)

One woman emphasised that she was worried about the baby, and that it was reassuring to be told that the foetus' needs are fulfilled despite the mother not eating much.

> "My doctor told me that no matter how often you vomit, the baby inside you takes what it needs, anyway. That is good to hear, because when I came to the ultrasound appointment in week seven or whatever, I had pictured a starved little lemon inside me." (W2)

Medicines – something for others, not for me

The participants were generally very sceptical to medicines use while pregnant. Avoidance was sought due to fear of teratogenic effects with references to the Thalidomide tragedy during the 60's. Some of the participants had the impression that also the GPs are reluctant to treat NVP with medicines due to fear of teratogenic effects, in contrast to their experience with the specialist health service who prescribed medicines when needed. Though the participants themselves had made the decision not to use medicines, they made it clear that they realised that the choice of treatment of NVP is individual. The question of treatment seemed to depend on how much one

can bear of the nausea's negative impact on social, occupational and daily life functioning, with the threshold set generally high.

> "I do not feel like medicating my discomfort, not when I can actually manage to eat at least something.[…]. But I do not have anything against others who want to medicate their nausea, or who are in need of medicines. Because I cannot know other people's needs, I only know what is right for me. […] I would never forgive myself if something happened to the baby just because I couldn't stand the nausea." (W6)

In contrast to the reluctance to use medicines, one woman, who had HG for the second time, thought that the GPs were too restrictive and that they delayed the use of medicines too long.

> "Women lose a lot of weight and get dehydrated. I don't think it should be like that considering you are carrying a child. I think it is important to have some quality of life despite having NVP." (W8)

Graded sick leave - something that is helpful

Most of the participants had been on sick leave due to their NVP. They had good experience with sick leave as helpful to reduce stress which was experienced as a trigger. Managing to keep a part time position, however, was emphasised as positive, as this enabled some social contact. To get off the couch and to think of other things than NVP for a while could be helpful. Otherwise, as one woman said, you will easily feel isolated, and a bit blue.

> "I think that, if one can manage, it would be best to be on graded sick leave. To be able to get some social input. And to get something out of the day, and get your thoughts on to

something other than nausea. Because you get very easily focused on the nausea lying on the couch the whole day." (W10)

The GPs

Emphasising normality

The GPs pointed out that due to NVP being one of many subjects on the list for the first pregnancy consultation, there is limited time to ask follow-up questions on how the pregnant women are handling their NVP. A box is typically ticked if nausea is confirmed, and unless the women have specific questions, the subject is left at that. If the women expressed concern with regards to NVP, the participants highly agreed on the importance of normalising the condition and assuring the woman that it is not harmful and not a disease.

> "I think it is very important to normalise it. NVP is not a disease, it is something to be expected while being pregnant." (GP2)

The dilemma of prescribing sick leave– appraised by the women, criticised by NAV

Sick leave was presented as a dilemma. A scenario, having the Norwegian Labour and Welfare Administration (NAV) on one side, demanding a more restrictive policy for sick leave, and the women on the other side, begging for sick leave, was described. They were also afraid that they might lose the patient if they denied the woman to go on sick leave.

"According to NAV it's all about the observations you do.[…] But that's the "NAV-world", and we work in another world. Our job is to build a relationship based on trust. If we had to doubt all patients who come and tell this kind of stories, it won't work out." (GP6)

Participants expressed a wish for an objective instrument to measure symptoms of NVP as supportive documentation of the reason for issuing sick leave.

The participants had generally a low threshold to prescribe sick leave, if the women were struggling with NVP. It was spontaneously mentioned by the participants when they were discussing treatment of NVP in general, giving the impression of sick leave being viewed by the GPs as one of the first interventions which was tried against NVP when action had to be taken, often without concomitant prescription of medicines.

"I don't think I have experienced that a tablet is what enable them to go to work. The result is sick leave anyway. They have sometimes been given a prescription in addition, to relieve the symptoms." (GP3)

Treatment with medicines is the next step – or is it?

When the participants were asked about interventions against NVP, they all agreed that advice on dietary and life style changes was a natural starting point, and something they seemed to be confident of giving. However, in their experience such measures were not of much help.

"A woman with NVP, had tried everything, and nothing helped. She had biscuits on the night table, eating just after waking up in the morning etc.. It didn't exactly provide her with much relief." (GP8)

The GPs expressed reluctance to use of medicines in the treatment of NVP. However, if dietary and life style changes and/or sick leave were insufficient, the participants seemed to agree on medicines being the next step. Medicines were only considered if the woman had too much time lost from work, or was close to admission to hospital due to NVP.

"Treatment is something that is being considered if the condition evolves to a great extent, but before the women are admitted to hospital due to electrolyte imbalance. When you feel you are in that phase where admission to hospital needs to be prevented". (GP2)

"Mmmhm." (GP3, GP4, GP5 nodding in agreement.)

It was expressed that they did not feel comfortable prescribing medicines against NVP due to the awareness of the teratogenic potential of use of medicines during first trimester, with references made to Thalidomide. Some of the GPs also agreed that they didn't believe in the effect of medicines against NVP.

"You may try very carefully with medications with no promise to the women that this is final quick-fix. They may as well not work." (GP5)

One GP even claimed that the cases which needed pharmacological treatment should be referred to the hospital and, consequently, that pharmacological treatment of NVP is outside the GP's area of responsibility.

> "I do believe that when it has come so far that they are in need for treatment because the
> NVP constitutes a health risk, we refer them to the hospital." (GP10)

The participants missed a "go-to medicine", a medicine that has NVP as one of the listed indications, especially in the light of EMA's warning against metoclopramide.

Discussion

Principal findings

The participants, both the pregnant women and the GPs in this study, elaborated on many issues related to nausea and pregnancy care. The call for help due to great distress seemed to be in conflict with the women's own scepticism to use of medicines. The women were concerned about potential harmful effects of medicines when used during pregnancy, and therefore tried to avoid use. They had rather negative experiences of the meeting with health care professionals in relation to NVP feeling that their distress due to nausea was not taken seriously. On the other hand, the GPs expressed that it was important to normalise NVP. The GPs seemed unsure about how to treat NVP when dietary and lifestyle interventions were insufficient. Though medicines were considered as the next step, the overall attitude among the GPs was to avoid medicines against NVP, mainly due to fear of teratogenicity. Below we discuss the strengths and limitations of the study design and the impact of our findings.

Strengths and limitations

Although this study is not generalizable beyond the participants in this setting, the data provides valuable insight into thoughts and attitudes among GPs and pregnant women that may be useful

for GPs and other health care personnel in contact with this patient group. A focus group design was chosen as this is considered well suited to study attitudes and experiences among a group of people within a specific milieu (eg. health care personnel or patients) [29]. It is an efficient method to gather data, and it also provides some quality control through the participants own tendency to react to and balance out extreme views [30]. The interaction taking place within groups, which is considered to be the hallmark of focus groups as a method [31], was specifically sought to help unveil concerns and priorities which may explain behaviour patterns [27]. Due to slow recruitment among pregnant women, a solely strategic sampling was hindered, but still the sample turned out quite diverse. Though the women were in general highly educated, the age and parity varied among the participants. The high level of education may act as a limitation. However, the women without a high education did not seem restrained and were well accepted in the group, possibly because they had pregnancy and nausea in common.

Our sample among GPs is relatively diverse, with varying age and gender. However, eight GPs had less than five years of experience. This may partly explain the participating GPs' uncertainty about the choice of treatment after dietary and life style advice was given. Another possible limitation is that the groups of GPs belonged to the same educational group, which may result in withholding conflicting point of views. However, the dynamic in the groups during the sessions was good, and contradictory statements seemed to be well tolerated. The groups were used to discuss different topics during their normal educational sessions, and the participants seemed comfortable with the setting. Educational groups which do not have a positive group dynamic would probably not accept an invitation to participate in a focus group study like this.

Due to slow recruitment, only two focus group discussions were conducted with each category of participants. This is an explorative study with the intention to obtain new insight into the attitudes

behind the rationale of treatment of NVP among both the receiver of the care and the caregiver, not to give a full description that covers the complete picture, in accordance to Malterud [28]. Based on the resulting information-rich data and the broad spectrum of themes that were uncovered, it was considered that two groups were adequate. However, there is always the possibility that conducting more group discussions might have brought up other relevant themes than those covered by this study.

Discussion of the findings

The pregnant women missed a deeper understanding of and acknowledgement from health care personnel for how debilitating nausea can be. The women's call for acknowledgement does not seem to be heard among the GPs who rather strongly agreed on the importance of normalisation of the symptoms of NVP. The GPs had good intentions by having this focus, as they thought it was important to reassure the patient that nausea is not harmful. However, it is our impression that the women and the GPs talk at cross purposes. The focus on normalisation was interpreted by the women as if the GPs did not take them seriously, especially when the GPs did not follow up with a proper clinical evaluation of the women's symptoms. Due to the high prevalence of nausea and a busy schedule for the first pregnancy consultation, the GPs admitted that nausea was often just confirmed and not carefully assessed. A study of HG patients from 2000, found that a high level of patient satisfaction was associated with women's perceptions that physicians believed in their descriptions of their symptoms [32]. Low level of belief in the patients may result in delayed intervention, and consequently affect the time for recovery [32], illustrating the importance of a good patient-GP relationship. This experienced lack of understanding of NVP among health care personnel was also described by Locock et al. in a study conducted in 2003-2004 illustrating minimal change in the situation over the last decade [6]. The well-known fact that nausea is very

common during pregnancy and most often self-limiting, may partly explain why this complaint gets so little attention. Also, national and international guidelines stress the importance of reassuring the women that nausea is a normal part of pregnancy [25, 26, 33]. However, there are several studies that describe NVP's negative impact on the women's wellbeing resulting in poor quality of life, symptoms of depression, and even elective termination of an otherwise wanted pregnancy [8-10, 34]. Locock et al. concluded that NVP was as disruptive for everyday life as a chronic disease [6]. Furthermore, 35% are clinically affected of NVP and NVP accounts for 23% of all sick leaves during pregnancy [2, 5, 13]. About 1% develops HG [4], which in most cases leads to hospitalisation and its related costs for the individual and the society [5, 12]. HG has also been associated with giving birth to low birth weight infants [35]. The participating GPs demonstrated a low awareness of the negative impact of NVP.

While the women had a clear call for help, they had a rather mixed message with respect to what kind of help they wanted. On one hand they criticised the GPs for not offering any prescription of medicines, but on the other hand, they were clearly sceptical to take medicines due to being pregnant.

The women did not judge others for using medicines, but tried to the utmost to avoid use themselves. It was a question of how much they could bear in order to protect their child from the perceived harmful effects of the medicines. This is in line with previous findings [20] and is probably due to the previously described overestimation of risk of medicine use among pregnant women [22]. Referral to the Thalidomide tragedy was made by pregnant women as well as GPs. Though one GP stated that pharmacological management of NVP was seen to be a specialist's task, not a GP's, the other GPs agreed that pharmacological treatment was the next step. However, they seemed wary of treating NVP with medicines due to fear of teratogenic effects.

This is in line with publications from UK [16], but is a paradox as there is available evidence supporting the safety of use during pregnancy of antiemetics [36]. The GPs expressed that medical treatment of NVP was mainly considered after progression of symptoms to become quite severe. The sceptical attitude to medicines among the women in combination with the normalisation and lack of evaluation of symptoms, and the reluctant attitude to treatment among the GPs, may prevent the question of treatment from being raised during the patient-GP encounter. HG is likely to be part of the continuum of nausea and vomiting during pregnancy [18]. The literature indicates that failure of early intervention against NVP, increases risk for hospitalisation due to HG [37, 38], illustrating the importance of identifying those women in need of treatment at an early stage. Hence, North American guidelines recommend early intervention to prevent progression to HG and more serious complications, including hospitalisation [17, 18]. Our results indicate that pregnant women requiring medical treatment against nausea would probably need comprehensive information and reassurance that there are treatment options which are considered to be effective and safe during pregnancy, before they would consider taking medicines. But before the participating GPs can take this position, they must obtain present evidence based knowledge about and confidence in available treatment options.

Improving quality of life during pregnancy and ability to maintain day-to-day activities for women with NVP should be reason enough for a GP to consider treatment. GPs meet women early in their pregnancy and have the opportunity to start symptom management at an early stage. It is recommended to communicate positive expectations regarding the outcome of a treatment to apply the placebo effect as a supplement to the verified treatment [39]. This contrasts the findings in this study where some GPs expressed little confidence in the treatment options they suggest to pregnant women.

The GPs missed clearer Norwegian treatment guidelines and had a call for a medicine with NVP as indication. This may explain the women's experiences of contradictory information from different health care personnel, and correction of prescriptions made by other physicians than the ones issuing it, which were described by the women who thought that this was scary and disturbing, rendering them even more sceptical. These findings indicate a lack of implementation of already existing guidelines and a need for clearer and stepwise guidelines that are easily accessible, to ensure consistence between health care personnel involved with pregnancy care. Of note, Diclegis/Diclectin, a medicine consisting of an antihistamine in combination of pyridoxine, with NVP as approved indication is available in Canada and USA.

Most of the women had been on sick leave due to NVP, and had good experiences related to graded sick leave which made the women feel less isolated due to enabling social interaction with colleagues, and at the same time having time to rest to relieve the symptoms. Feelings of isolation have also previously been described in relation to NVP [7]. During the discussions with the GPs, sick leave was spontaneously mentioned when the moderator primarily addressed treatment. It was an impression that sick leave was an important part of the treatment regime applied by the GPs, probably as a consequence of a need for additional rest among women with NVP and the reluctance to use of medicines, with sick leave being viewed as a safe intervention from both parts. Sick leave often seems to be given without the concomitant prescribing of medicines that could give additional relief, or in some cases maybe enable the woman to work part time.

The question of prescribing sick leave was presented as a dilemma. This demonstrates awareness among the GPs who are trying to build an alliance with the women, and at the same time acknowledging the criteria set by NAV. This is in accordance with previous findings [40]. A lack of an objective measure of nausea to enable documentation for NAV on what grounds the

sick leave is being prescribed was mentioned in relation to the sick leave dilemma. The Pregnancy-Unique Quantification of Emesis (PUQE) scale has been translated to Norwegian and is included in the new national guideline for treatment of NVP [23, 41]. The PUQE scale serves as a tool to help objectify the women's NVP symptoms, enables classification of degree of nausea (mild, moderate and severe) and is helpful in evaluating the effect of various interventions [41]. However, the experience of nausea, even if classified to the same degree according to PUQE, may deviate between different individuals. Hence, the women's own experience should be acknowledged by the GPs and the women treated accordingly.

Conclusion

This Norwegian study identifies attitudes among both the participating GPs and pregnant women that may act as obstacles to appropriate care of women suffering from NVP. The GP's automatic normalisation of symptoms and lack of assessment of the burden of NVP is interpreted as the main obstacle to appropriate care for women suffering from this condition. Also the women's own scepticism to medical treatment while pregnant may hinder appropriate treatment when indicated. The pregnant women and the GPs talked at cross purposes; GPs normalisation of the symptoms made the women feel their distress due to NVP was trivialised by the GPs. Our results indicate that pregnant women requiring medical treatment against nausea would probably need comprehensive information and reassurance that there are safe treatment options for NVP, before they would consider taking medicines. However, the participating GPs showed reluctance to the use of medicines to treat NVP, and appeared to be insecure of the safety and the effectiveness of treatment.

Conflict of interest and funding

References:

1.   Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(2):e171-83.

2.   Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43(371):245-8.

3.   Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182(4):931-7.

4.   Vikanes A, Grjibovski AM, Vangen S, Magnus P. Variations in prevalence of hyperemesis gravidarum by country of birth: A study of 900,074 pregnancies in Norway, 1967—2005. Scandinavian journal of public health. 2008;36(2):135-42.

5.   Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. The New England journal of medicine. 2010;363(16):1544-50.

6.   Locock L, Alexander J, Rozmovits L. Women's responses to nausea and vomiting in pregnancy. Midwifery. 2008;24(2):143-52.

7.   O'Brien B, Evans M, White-McDonald E. Isolation from "being alive": coping with severe nausea and vomiting of pregnancy. Nurs Res. 2002;51(5):302-8.

8.   Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S220-7.

9.   Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol. 2000;40(4):397-401.

10.   Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol. 2000;21(3):129-36.

11.   Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. Curr Med Res Opin. 2007;23(4):833-40.
12.   Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(2):e149-60.
13.   Dorheim S, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. BJOG. 2013;(5):521-530.
14.   The Norwegian Welfare and Labour Administration. Sickness benefits for employees: The Norwegian Welfare and Labour Administration,; 2011 (accessed 19 August 2015). Available from: https://www.nav.no/en/Home/Benefits+and+services/Relatert+informasjon/Sickness+benefits+for+employees.283831.cms.
15.   The Norwegian Directorate of Health. Svangerskapskontroller [Pregnancy consultations]: helsenorge.no; 2014 (accessed 27 August 2015). Available from: https://helsenorge.no/gravid/svangerskapskontroller.
16.   Gadsby R, Barnie-Adshead T, Sykes C. Why won't doctors prescribe antiemetics in pregnancy? BMJ. 2011;343:d4387.
17.   Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24(10):817-31; quiz 32-3.
18.   Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12-24.
19.   Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth defects research Part A, Clinical and molecular teratology. 2012;94(1):22-30.
20.   Baggley A, Navioz Y, Maltepe C, Koren G, Einarson A. Determinants of women's decision making on whether to treat nausea and vomiting of pregnancy pharmacologically. J Midwifery Wom Heal. 2004;49(4):350-4.
21.   Koren G, Levichek Z. The teratogenicity of drugs for nausea and vomiting of pregnancy: perceived versus true risk. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S248-52.
22.   Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66(2):207-14.
23.   Norsk gynekologisk forening. Veileder i fødselshjelp [Obstetric guidelines issued by The Norwegian Gynecological Association]. 2014.
24.   Norsk Legemiddelhåndbok [Norwegian Medicines Handbook]. 2015 (accessed 09 April 2015). Available from: http://legemiddelhandboka.no/Terapi/søker/+%2Bsvangerskapskvalme/19493.
25.   Sosial og helsedirektoratet. Nasjonale faglige retningslinjer: Retningslinjer for svangerskapsomsorgen. [National guidelines for pregnancy care]. 2005.
26.   Norsk Elektronisk Legehåndbok [Norwegian Electronic Medical Handbook]. Norsk Helseinformatikk. 2015 (accessed 04 May 2015). Available from: http://legehandboka.no/.
27.   Smith F. Reasearch Methods in Pharmacy Practice. London: Pharmaceutical Press; 2002.
28.   Malterud K. Systematic text condensation: a strategy for qualitative analysis. Scand J Public Health. 2012;40(8):795-805.
29.   Malterud K. Kvalitative metoder i medisinsk forskning. En innføring. [Qualitative methods in medical reasearch. An introduction.]. 3rd ed. Oslo: Universitetsforlaget; 2011.
30.   Patton M. Qualitative evaluation and research methods. 2nd ed. Newbury Park: Sage Publications; 1990.
31.   Morgan DL. Focus groups as qualitative research. 2nd ed. Thousand Oaks: Sage Publications; 1997. 80 p.

32.   Munch S. A qualitative analysis of physician humanism: women's experiences with hyperemesis gravidarum. Journal of perinatology : official journal of the California Perinatal Association. 2000;20(8 Pt 1):540-7.

33.   National Collaborating Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman: National Institute for Health and Clinical Excellence (NICE); 2008 (accessed 19 March 2015). Available from: http://www.nice.org.uk/guidance/cg62/resources/guidance-antenatal-care-pdf.

34.   Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol. 2001;22(1):7-12.

35.   McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. International Journal of Women's Health. 2014;6:719-25.

36.   Smith J, Refuerzo J, Ramin S. Treatment and outcome of nausea and vomiting of pregnancy. UpToDate. 2014.

37.   Lamm SH. The epidemiological assessment of the safety and efficacy of Bendectin. In: Koren G, Bishai R, editors. Nausea and vomiting of pregnancy: sate of the art 2000. Toronto: Motherisk; 2000. p. 100-3.

38.   Neutel CI. Variation in rates of hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada. In: Koren G, editor. Nausea and Vomiting of Pregnancy : State of the Art 2000. Toronto, Canada: Motherisk; 2000.

39.   Bystad M, Bystad C, Wynn R. How can placebo effects best be applied in clinical practice? A narrative review. Psychology research and behavior management. 2015;8:41.

40.   Nilsen S, Malterud K, Werner EL, Maeland S, Magnussen LH. GPs' negotiation strategies regarding sick leave for subjective health complaints. Scand J Prim Health Care. 2015(0):1-7.

41.   Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. J Obstet Gynaecol Can. 2009;31(9):803-7.

Table 1 Sample distribution of study participants

Category	Variables	N
Pregnant women		
Age	Range	24 – 37 years
Education	High school/vocational school	1
	Bachelor degree/college	4
	Master degree or higher	5
Parity	No previous live birth	6
	≥1 previous live births	4
GPs		
Gender	Female	5
	Male	5
Age	Range	27 - 48 years
Years of experience	≤ 5 years	8
	> 5 years	2