Eur J Clin Pharmacol (2016) 72:593–604
DOI 10.1007/s00228-016-2012-6

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Treatment of nausea and vomiting during pregnancy — a cross-sectional study among 712 Norwegian women

Kristine Heitmann[1] · **Anja Solheimsnes**[1] · **Gro C. Havnen**[2] · **Hedvig Nordeng**[3] · **Lone Holst**[1]

Received: 6 November 2015 / Accepted: 12 January 2016 / Published online: 27 January 2016

Abstract
Purpose The purposes of this study were to investigate the treatments used for nausea and vomiting of pregnancy (NVP) according to NVP severity among Norwegian women and to assess whether maternal characteristics and attitudes were related to the use of pharmacological treatment of NVP.
Methods This is a cross-sectional Web-based study. Pregnant women and mothers with children ≤1 year of age were eligible to participate. Data were collected through an anonymous online questionnaire accessible from November 10th, 2014 to January 31st, 2015.
Results In total, 712 women were included in the study, of which 62 (8.7 %), 439 (61.7 %) and 210 (29.5 %) had mild, moderate and severe NVP, respectively, according to the Pregnancy-Unique Quantification of Emesis (PUQE) classification. A total of 277 (38.9 %) women had used one or more antiemetics, of which meclizine, closely followed by metoclopramide, was the most commonly used. Different drug utilisation patterns were found between the groups of women with mild, moderate and severe NVP. Many with moderate or severe symptoms did not use any pharmacological treatment (70.2 and 32.9 %, respectively). Sick leave was given without initiating medical treatment in 266 (62.1 %) women. The women's beliefs about medicines had an important impact on their use of medicines for NVP.
Conclusions A large proportion of women suffered from moderate to severe symptoms of NVP, many of whom did not receive any pharmacological treatment. Many women, who had been on sick leave due to NVP, were not prescribed medicines.

Keywords Morning sickness · Hyperemesis gravidarum · Pregnancy · Drug therapy · Meclizine · Metoclopramide

Introduction

Nausea in pregnancy affects approximately 70 % of all pregnant women to various degrees [1]. Around 50 % experience additional vomiting [2–4]. Typically, the symptoms initiate in the 6th pregnancy week, with a peak in intensity around week 8–13, before gradually declining during the second trimester [2, 3, 5]. Symptoms of nausea and vomiting in pregnancy (NVP) range from mild to severe. The most severe form of NVP is termed hyperemesis gravidarum (HG) often necessitates hospitalisation and affects 0.3–2 % of all pregnant women [6]. The prevalence of HG was reported to be 1.4 % in the Medical Birth Registry of Norway [7].

Various guidelines to treatment of NVP exist [8–15]. All guidelines recommend starting with dietary and lifestyle changes: avoid triggers, fatty or spicy foods, avoid an empty stomach, take frequent small meals, fluids between meals, and/or keep crackers at bedside. Antihistamines, often in combination with vitamin B6 and pyridoxine, are recommended as first-line treatment if dietary and lifestyle changes fail. Trying a

Electronic supplementary material The online version of this article (doi:10.1007/s00228-016-2012-6) contains supplementary material, which is available to authorized users.

✉ Kristine Heitmann
kristine.heitmann@igs.uib.no

[1] Department of Global Public Health and Primary Care, University of Bergen, P-Box 7804, N-5018, Bergen, Norway

[2] Regional Medicines Information and Pharmacovigilance Centre (RELIS), Oslo University Hospital, Oslo, Norway

[3] PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway

D_2-antagonist is usually the next step, before a $5HT_3$-antagonist is considered. Glucocorticoids are reserved for refractory patients that do not respond to anything else and are not recommended to use before pregnancy week 10 [9, 16].

Because NVP is referred to as mild, transient and self-limiting in many guidelines, there may be a tendency to trivialize the symptoms. National and international guidelines stress the importance of reassuring women that nausea is a normal part of pregnancy, stating that medical interventions are rarely necessary [10, 12, 13]. Women report that they have experienced not being taken seriously by health care personnel when presenting with NVP [17, 18], though previous studies report that NVP greatly interferes with the women's lives, negatively affecting their quality of life, everyday life, social and occupational functioning, relationship with partner and caring for children [19–22]. Women with severe symptoms report that NVP has major impact on family planning, with several women reporting that they do not want to be pregnant again, and some women are even reporting terminations of otherwise wanted pregnancies to end the severe suffering due to NVP [21, 23, 24]. However, Canadian and American guidelines recommend early treatment of the symptoms of NVP to reduce patient suffering, costs related to hospitalizations, contacts with pregnancy care units and sick leave, arguing that early symptoms are easier to treat [8, 11].

There are approximately 60,000 births in Norway annually. Norwegian employees are entitled to sickness benefits equivalent to full wages if occupationally disabled due to own illness [25]. The sick leave may be fulltime or graded (part time) [25], e.g. working 50 % and being paid sickness benefits equivalent to 50 % wages. Furthermore, the country has a well-functioning pregnancy care program that is free of charge. All residents in Norway have been assigned a personal general practitioner (GP). Pregnant women have the right to nine free consultations with either a general practitioner or a midwife [26], of which the first consultation usually takes place between pregnancy week 8 and 12. We think that this system should facilitate early detection of NVP symptoms and therefore also the management of these symptoms. However, a recent study showed that Norwegian women with NVP used medicines to a lesser extent (12 %) than women from other countries such as Sweden (34 %), Iceland (28 %), France (38 %) and Canada (42 %) [27].

Attitudes to medicines are likely to impact women's decisions whether to use any medicines or complementary and alternative medicine (CAM) to treat NVP or not and also affect their choice of treatment. If attitudes prevent women from using a necessary medicine for NVP, this may influence their physical and psychological well-being. This is especially important for those women with more severe NVP symptoms, who, if not treated properly, may be admitted to hospital due to dehydration and electrolyte imbalance [28].

To the best of our knowledge, no study has investigated the treatment of NVP according to the severity of symptoms in a Scandinavian population.

In this study, we investigated the treatments used for NVP according to the NVP severity defined by the 24-h Pregnancy-Unique Quantification of Emesis scale (PUQE) 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.

Material and methods

Study design and data collection

We carried out a cross-sectional Web-based study. Pregnant women and mothers with children less than 1 year of age, who had experienced NVP in their latest pregnancy, were eligible to participate. Data were collected through an anonymous online questionnaire administered by SurveyXact and accessible within the period of 10th of November 2014 to 31st of January 2015. The questionnaire was accessible via banners (invitations to participate in the study) on national websites and social networks commonly visited and consulted by pregnant women and/or new mothers ("altformamma.no", "mamma.no", "tryggmammamedisin.no" and "foreldre.no's" Facebook page) and on a Facebook page specifically created for this study, enabling the link to be shared on social media. A pilot study was carried out ($n = 5$), eliciting only minor changes to the questionnaire, increasing free text entry fields and adding free text entry fields to enable reporting more details with respect to specific questions. We also had to change the stated time needed to answer the questionnaire in the information letter shown to the women before entering the questionnaire.

Collected data were scrutinized for the presence of potential duplicates (based on reported sociodemographic characteristics) but none were identified.

Measures

The questionnaire included questions on maternal characteristics, NVP and treatments used for NVP, conventional medicines, CAM and hospitalisation. The women's beliefs about medicines and alternative treatments were also explored.

Classification of NVP, severity of symptoms

NVP was measured and classified into three groups of different severity by using the 24-h PUQE [28]. PUQE consists of three criteria to assess the severity of NVP, the numbers of hours of nausea, number of episodes of retching and number of episodes of vomiting within the last 24 h. Each criterion has five options which are scored from 1 to 5 points. The PUQE

score is calculated by adding the values from each category. The total score ranges from 3 to 15 points. The severity of nausea is classified according to the PUQE score: mild ≤6 points; moderate 7–12 points and severe ≥13 points. PUQE has been validated to correlate with risk of hospitalisation due to severe NVP, increased health care costs because of NVP, reduced well-being/QOL, insufficient nutritional intake and inability to take iron supplements [29, 30]. A Norwegian translated version of PUQE was recently validated [30]. The women were asked to recall the extent of their NVP for a typical 24 h in the period with the most severe symptoms.

Treatments used for nausea

The participants were asked if they had made any changes in lifestyle or diet to reduce the nausea, if they had used any medicines, vitamin supplements or alternative treatments for nausea or if they had been treated in the hospital for nausea. In affirmative response, the participants were presented a list of commonly used therapies against nausea (Dietary and life style changes; antiemetics, such as Postafen® (meclizine), Afipran® (metoclopramide), Zofran® (ondansetron), Stemetil® (prochlorperazine), Phenergan® (promethazine) and Largactil® (chlorpromazine); alternative treatments, such as herbal products containing ginger, peppermint and raspberry leaves or acupuncture and acupressure (SeaBand®), homeopathy; vitamins, such as vitamin B6, B1, B12, folic acid and multivitamins; treated at the hospital). If the participants had used a product not part of the pre-specified list, the therapy could be reported in free-text entry fields. Duration of therapy, dosage and who initiated the treatment could also be reported.

Attitudes towards medicines and alternative treatments

Six pregnancy-specific statements were presented to the women (S1–S6), of which three were general: (S1) "I have a higher threshold for using medicines when I am pregnant than when I'm not pregnant"; (S2) "It is better for the foetus that I use medicines and get well than to have an untreated illness during pregnancy"; and (S3) "Pregnant women should preferably use herbal remedies than conventional medicines". These statements originate from the previous research [31, 32]. In addition, the women were presented the following three NVP-specific statements: (S4) "Even though I had NVP I chose to refrain from using medicines for nausea just to be safe"; (S5) "I was anxious for how the medicines affected the foetus" and (S6) "I used less medicine than needed for nausea due to being pregnant".

The study participants could tick "strongly agree", "agree", "uncertain", "disagree" or "strongly disagree" for each of the pregnancy-specific statements. In the analyses, these variables were trichotomized: "disagree" or "strongly disagree" = "disagree", "uncertain" = "uncertain", "agree" or "strongly agree" = "agree". In addition, the women could answer "doesn't apply to me".

Maternal characteristics

The following variables were explored in relation to the use of conventional medicines: severity of NVP; parity; maternal age; body mass index (BMI); smoking during pregnancy; use of folic acid; marital status; education and working status. Sociodemographic variables are categorized as presented in Table 1. The severity of nausea was also explored in relation to the use of CAM and hospitalisation due to NVP.

Statistical analyses

Univariate and multivariable logistic regression analyses were performed to explore the potential significant associations between the maternal characteristics listed in Table 1 and the use of conventional medicines for NVP. Odds ratios (ORs) are presented with 95 % confidence intervals (CIs). All variables in Table 1 were included in the multivariable models.

Descriptive statistics were used to calculate the prevalence of conventional and herbal medicines use for NVP during pregnancy and presented as percentages.

Univariate and multivariable logistic regression analyses were also used to explore the relationship between the use of conventional medicines and general attitudes. First, univariate analyses were performed. Then full multivariable 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 the removal of the variable caused a >10 % change in the effect estimates.

Chi-square tests (χ^2) were performed to investigate the relationship between the severity of nausea and beliefs. Significance level was set to $p < 0.05$.

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 read the description of the study. This included the study objectives, the participants' right to withdraw at any time and contact information to members of the research group. In addition, the women had to answer the following question: "Are you willing to participate in the study?" If the woman ticked "yes" as the answer, this was considered an informed consent. Informed consent was obtained from all individual participants included in the study. The study was approved by the Regional Ethics Committee, Region West in Norway. The Norwegian Social Science Data Services were also consulted.

Table 1 Characteristics of the study population according to the use of conventional medicines for NVP

	Total *N* = 712 *n* (%)	Use of NVP medicines *N* = 277 *n* (%)	Use of NVP medicines vs. no use Adjusted OR[a] (95 % CI)
Severity of nausea, PUQE[d]			
Mild	62 (8.7)	5 (8.1)	*0.2* (*0.1–0.5*)
Moderate	439 (61.7)	131 (29.8)	1
Severe	210 (29.5)	141 (67.1)	*5.1* (*3.5–7.4*)
Parity			
0 previous live births	382 (53.7)	137 (49.8)	1
≥1 previous live births	327 (45.9)	138 (50.2)	1.3 (0.9–1.9)
Age, years			
Under 25	145 (20.4)	64 (23.1)	1.3 (0.8–2.2)
25–29	273 (38.3)	99 (35.7)	1
30–39	281 (39.5)	109 (39.4)	1.3 (0.9–2.0)
Over 40	13 (1.8)	5 (1.8)	1.1 (0.3–4.0)
Body mass index (BMI)[c]			
Underweight	33 (4.6)	16 (5.8)	1.8 (0.8–4.0)
Normal weight	421 (59.1)	158 (57.0)	1
Overweight	139 (19.5)	54 (19.5)	1.1 (0.7–1.7)
Obese	118 (16.6)	49 (17.7)	1.0 (0.6–1.6)
Smoking			
No	684 (96.1)	262 (94.6)	1
Yes	27 (3.8)	15 (5.4)	2.0 (0.8–4.9)
Use of folic acid			
Before the pregnancy	141 (19.8)	45 (16.2)	0.9 (0.6–1.5)
During pregnancy	342 (48.0)	139 (50.2)	1
Before and during pregnancy	191 (26.8)	73 (26.4)	1.1 (0.7–1.6)
No	37 (5.2)	19 (6.9)	1.4 (0.6–3.1)
Marital status			
Married/cohabitating	661 (92.8)	253 (91.3)	1
Not married/cohabiting	51 (7.2)	24 (8.7)	1.7 (0.9–3.5)
Education[b]			
Primary	29 (4.1)	10 (3.6)	0.6 (0.2–1.5)
Secondary	191 (26.8)	87 (31.4)	1.1 (0.7–1.7)
Bachelor degree	292 (41.0)	117 (42.2)	1
Master degree	170 (23.9)	49 (17.7)	*0.6* (*0.4–1.0*)
Other	30 (4.2)	14 (5.1)	1.3 (0.6–2.9)
Work situation			
Student	57 (8.0)	28 (10.1)	1.5 (0.8–2.9)
Employed	570 (80.1)	220 (79.4)	1
Unemployed	53 (7.4)	17 (6.1)	*0.5* (*0.2–1.0*)
Other	32 (4.5)	12 (4.3)	1.0 (0.4–2.3)

Numbers do not always add up due to missing numbers. Italic effect estimates indicate significant findings.

Abbreviations: *NVP* nausea and vomiting of pregnancy *OR* odds ratio, *CI* confidence interval, *PUQE* Pregnancy-Unique Quantification of Emesis

[a] Adjusted for all other variables in the table

[b] Primary, ≤10 years of education (the Norwegian compulsory primary + secondary school) and secondary, 10–12 years (high school/upper secondary or vocational school)

[c] Body mass index (BMI) is the weight in kilograms divided by the square of the height in metres: underweight, <18.5 kg/m^2 ; normal weight, 18.5–24.9 kg/m^2 ; overweight, 25.0–29.9 kg/m^2 and obese ≥30 kg/m^2

[d] As classified by PUQE: mild ≤6 points; moderate 7–12 points and severe ≥13

Results

In total, 712 women completed the questionnaire and were included in the study. There were 447 (62.8 %) women who were pregnant at participation and 265 (37.2 %) who had given birth within the previous year. Of the women who were pregnant, 155 (21.8 %), 196 (27.5 %) and 96 (13.5 %) women were in first, second and third trimester, respectively. The study participants were comparable to the general Norwegian birthing population with respect to the geographic living area, age, marital status, folic acid use and smoking status (Appendix 1) [33, 34]. However, a larger percentage of women included in the study had higher education than in the general birthing population. Among the study participants, 41.0 and 23.9 % had a bachelor or master degree, respectively, while the numbers for women aged 20–49 years in the general population were 35.2 and 11.8 %, respectively [34].

While the onset of symptoms for most women (65.7 %) was during pregnancy week 5–7, the time when symptoms resolved was more varied (Appendixes 2 and 3). Among the 425 women who reported that their symptoms had resolved by the time of participation in the study, 192 (45.2 %) reported that the symptoms resolved by pregnancy week 16. Meanwhile, 147 (34.6 %) women were still experiencing symptoms around pregnancy week 20. Median duration of NVP was 12 weeks (range 2–40) (Appendix 4).

According to the PUQE classification, 62 (8.7 %) of the women had mild NVP, while 439 (61.7 %) and 210 (29.5 %) suffered from moderate and severe NVP, respectively. A total of 193 (27.1 %) women reported with a diagnosis of HG, 117 (16.4 %) reported electrolyte disturbances and 108 (15.2 %) had been treated for NVP in hospital.

The women had used a variety of different treatments for NVP (Table 2). The vast majority, 658 women (92.4 %), had tried dietary and lifestyle changes. CAM was used by 384 (53.9 %) women, of which 188 women had used both conventional medicines and CAM. Ginger and acupressure were the most commonly used CAM; however, quite many had also used acupuncture. Among the 384 women using CAM, 165 (43.0 %) had used one type of CAM, the majority being ginger or acupressure, and 139 (36.2 %) had used two types of CAM, most frequently a combination of ginger and acupressure (82 women, 59.0 %). Maximum number of types of CAM used was seven.

A total of 277 (38.9 %) women had used one or more medicines for NVP. The most commonly used medicine for NVP was meclizine, closely followed by metoclopramide. Ondansetron, promethazine, prochlorperazine and chlorpromazine were all used by less than 10 % of the participants. Though most of the women had used only one medicine (168/277) or two medicines (60/277), maximum number of medicines used was six. Among the 168 (23.6 %) women who had only used one medicine, 90 (53.6 %) had used an antihistamine (meclizine, 78 (46.4 %) and promethazine, 12 (7.1 %)) and 59 (35.1 %) had used metoclopramide. Among the women who had used two medicines, the most common combination was meclizine and metoclopramide (32 women, 53.3 %).

The vast majority of the women who had used meclizine or metoclopramide had used it for 1 month or less (Table 3). This also applied for the other treatments, including the CAMs. However, ondansetron was used for 4 months or longer by 26 % of the users. Of note, 83 (56 %) of the women that had used metoclopramide used it for 1 week or more. Among the women pregnant at the time of participation, 67 women (15.0 %) had used metoclopramide, of which 38 (56.7 %) women had used it for 1 week or more.

While the treatment with meclizine and metoclopramide was most often initiated by a general practitioner, treatment with ondansetron and promethazine was most commonly initiated by a hospital doctor or a gynaecologist (Table 3). Sub-analyses revealed that women who were hospitalised for NVP were 27 times more likely to have used ondansetron compared to non-hospitalised women (crude OR = 26.8, 95 % CI = 13.4–53.6). Women with severe NVP were eight times more likely to use ondansetron than women with mild or moderate NVP (crude OR = 8.0, CI = 4.2–15.5). CAM treatments were most commonly initiated on women's own initiative.

Different drug utilisation patterns were found between the groups of women with mild, moderate and severe NVP, showing a gradient towards higher use of all medicines with increasing severity of NVP (Table 2). Medicines were used by 8.1, 29.8 and 67.1 % of women with mild, moderate and severe NVP, respectively. The number of medicines used also increased according to the severity of symptoms. While no women with mild NVP used more than one medicine, 39 (8.9 %) and 70 (33.3 %) women with moderate and severe NVP, respectively, had used two or more medicines. The severity of NVP was associated with the use of CAM (adjusted OR (95 % CI) for mild and severe NVP was 0.5 (0.3–0.9) and 2.6 (1.2–3.7), respectively, with moderate NVP as the reference group) and with admission to hospital due to NVP (adjusted OR (95 % CI) for mild and severe NVP was 0.2 (0.03–1.7) and 8.4 (5.1–13.8), with moderate NVP as the reference group) when adjusting for all other variables in Table 1. Adjusted analyses revealed that education, occupation and severity of NVP were factors predicting the use of medicines for nausea (Table 1).

In total, 108 (15.2 %) of the women had been treated in hospital due to NVP. Most of these women (76 women) had severe NVP as classified by PUQE and constitute 36.2 % of the women with severe symptoms. However, 31 (7.1 %) of the women classified by PUQE as having moderate NVP and one woman classified as having mild NVP had also been treated in hospital. Among the women with moderate NVP who were treated in hospital, 24 (77.4 %) had a PUQE score between 10 and 12.

Table 2 Use of various treatments according to the severity of NVP

	Severity of nausea, PUQE[a]			
	Total $N=712$ n (%)	Mild $N=62$ n (%)	Moderate $N=439$ n (%)	Severe $N=210$ n (%)
ANY TREATMENT[b]	475 (66.7)	32 (51.6)	342 (77.9)	191 (90.9)
Conventional medicines	277 (38.9)	5 (8.1)	131 (29.8)	141 (67.1)
Meclizine	168 (23.6)	4 (6.5)	75 (17.1)	89 (42.4)
Metoclopramide	148 (20.8)	0 (0.0)	65 (14.8)	83 (39.5)
Ondansetron	50 (7.0)	0 (0.0)	13 (3.0)	37 (17.6)
Promethazine	47 (6.6)	0 (0.0)	16 (3.6)	31 (14.8)
Prochlorperazine	29 (4.1)	0 (0.0)	7 (1.6)	22 (10.5)
Chlorpromazine	22 (3.1)	0 (0.0)	4 (0.9)	18 (8.6)
Vitamins	373 (52.4)	13 (21.0)	229 (52.2)	131 (62.4)
Folic acid	328 (46.1)	12 (19.4)	198 (45.1)	118 (56.2)
Multivitamins	184 (25.8)	6 (9.7)	112 (25.5)	66 (31.4)
Vitamin B12	71 (10.0)	3 (4.8)	44 (10.0)	24 (11.4)
Vitamin B6	69 (9.7)	4 (6.5)	41 (9.3)	24 (11.4)
Vitamin B1	38 (5.3)	2 (3.2)	19 (4.3)	17 (8.1)
CAM	384 (53.9)	20 (32.3)	219 (49.9)	145 (69.0)
Ginger	264 (37.1)	12 (19.4)	155 (35.3)	97 (46.2)
Acupressure (SeaBand)	245 (34.3)	5 (8.1)	136 (31.0)	104 (49.5)
Acupuncture	102 (14.3)	1 (1.6)	50 (11.4)	51 (24.3)
Peppermint	42 (5.9)	3 (4.8)	23 (5.2)	16 (7.6)
Raspberry leaves	21 (2.9)	0 (0.0)	12 (2.7)	9 (4.2)
Homeopathy	15 (2.1)	0 (0.0)	5 (1.1)	10 (4.8)
Treated in hospital due to NVP	108 (15.2)	1 (1.6)	31 (7.1)	76 (36.2)

Abbreviations: *PUQE* Pregnancy-Unique Quantification of Emesis, *CAM* complementary and alternative medicine

[a] As classified by PUQE: mild ≤6 points; moderate 7–12 points and severe ≥13

Treatments used by less than 2 % in the total population are not shown

[b] Including conventional medicines, vitamins, and CAM used for NVP and treatments at the hospital for NVP

Among the 712 women, 428 (60.1 %) women had been on sick leave due to NVP, of which 249 (58.2 %) had been on full-time sick leave, 64 (15.0 %) on part-time sick leave and 115 (26.9 %) on a combination of full- and part-time sick leave. In 49.3 % of the cases, the physician recommended sick leave, and in 45.8 %, the woman herself initiated leave. Sick leave was given without starting medical treatment in 266 (62.1 %) women, and only 37 (8.6 %) women started medical treatment before they went on sick leave. Among the women that had been on sick leave, 202 (47.2 %) did not use any medicines for NVP. Compared to women with mild symptoms, women with moderate and severe symptoms were significantly more likely to have been on sick leave (crude ORs, (95 % CI); moderate NVP, 8.9 (4.2–18.3) and severe NVP, 54.9 (23.3–129.8)).

Women's attitudes towards the three general pregnancy-specific statements were analysed for associations with the use of medicines (Table 4). Women who agreed with or were uncertain about the statement S2 ("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 compared to women who disagreed. The majority of the women (79.4 %) reported that they had a higher threshold for using medicines while being pregnant (S1), and only 29.6 % believed that the foetus would benefit from the mother taking a medicine to get well (S2).

The severity of symptoms was associated with some of the statements. There was a decreasing degree of agreement with statement S1 across severity of NVP: 93.1, 78.8 and 76.5 % who agreed with statement S1 had mild, moderate and severe NVP, respectively (χ^2, $p<0.05$). The same pattern was observed for statement S4 ("Even though I had NVP I chose to refrain from using medicines for nausea just to be safe"): 71.4, 60.4 and 32.8 % of the women who agreed with the statement had mild, moderate and severe NVP, respectively, (χ^2, $p<0.05$).

Among women who had used conventional medicines ($n=277$), a substantial proportion of the women reported that

Table 3 An overview of the duration of treatment of conventional medicines and CAM and who initiated the treatment

Treatment	Total $N = 712$ n (%)	Duration of treatment[b]			Who initiated treatment				
		≤1 month	5 weeks to 3 months	≥4 months	General practitioner	Hospital doctor/ gynaecologist	Midwife	Own initiative	Other
Conventional medicines									
Meclizine	168 (23.6)	114 (67.9)	36 (21.4)	10 (6.0)	100 (59.5)	38 (22.6)	1 (0.6)	22 (13.1)	9 (5.4)
Metoclopramide	148 (20.8)	101 (68.2)	21 (14.2)	17 (11.5)	95 (64.2)	38 (25.7)	2 (1.4)	8 (5.4)	6 (4.1)
Ondansetron	50 (7.0)	24 (48.0)	10 (20.0)	13 (26.0)	14 (28.0)	32 (64.0)	1 (2.0)	1 (2.0)	2 (4.0)
Promethazine	47 (6.6)	26 (55.3)	8 (17.0)	9 (19.1)	21 (44.7)	23 (48.9)	–	1 (2.1)	2 (4.3)
CAM									
Ginger	264 (37.1)	181 (68.6)	42 (15.9)	17 (6.4)	12 (4.5)	3 (1.1)	9 (3.4)	212 (80.3)	28 (10.6)
Acupressure[a]	245 (34.3)	130 (53.1)	72 (29.3)	24 (9.8)	7 (2.9)	2 (0.8)	6 (2.4)	198 (80.8)	32 (13.1)
Acupuncture	102 (14.3)	72 (70.6)	16 (15.7)	7 (6.9)	5 (4.9)	2 (2.0)	15 (14.7)	62 (60.8)	18 (17.6)
Peppermint	42 (5.9)	24 (57.1)	8 (19.0)	4 (9.5)	2 (4.8)	–	3 (7.1)	28 (66.7)	9 (21.4)

Treatments used by less than 5 % are not shown

Abbreviations: *CAM* complementary and alternative medicine

[a] SeaBand

[b] Numbers do not always add up due to missing numbers

they were anxious for how the medicines affected the foetus (S5) ($n = 216$, 78.0 %), and that they used less medicine than needed for nausea due to being pregnant (S6) ($n = 165$, 59.6 %). Also, among women with severe NVP who had used conventional medicines ($n = 137$), 84 (61.3 %) women agreed that they used less medicines than needed due to being pregnant (S6).

Discussion

To our knowledge, this is the first study to investigate the treatment of NVP based on the degree of NVP according to severity and attitudes in a Scandinavian country. Several findings have shown clinical importance. We found a large proportion of women who continue to experience moderate and

Table 4 Beliefs according to treatment with conventional medicines

Statements	Total N_1 n (%)	Conventional medicines N_2 n (%)	Use of conventional medicines vs. no use Adjusted ORs (95 % CI)
S1. I have a higher threshold for using medicines when I am pregnant than when I'm not pregnant ($N_1 = 688$, $N_2 = 268$)[a]			
Disagree	108 (15.7)	44 (16.4)	1
Agree	546 (79.4)	204 (76.1)	1.0 (0.6–1.6)[b]
Uncertain	34 (4.9)	20 (7.5)	1.6 (0.7–3.7)[b]
S2. It is better for the fetus that I use medicines and get well than to have an untreated illness during pregnancy ($N_1 = 697$, $N_2 = 276$)[a]			
Disagree	180 (25.8)	49 (17.8)	1
Agree	206 (29.6)	110 (39.9)	*3.3 (2.1–5.3)*[b]
Uncertain	311 (44.6)	117 (42.4)	*1.6 (1.0–2.5)*[b]
S3. Pregnant women should preferably use herbal remedies than conventional medicines ($N_1 = 680$, $N_2 = 265$)[a]			
Disagree	359 (52.7)	143 (54.0)	1
Agree	67 (9.9)	25 (9.4)	0.9 (0.5–1.7)[c]
Uncertain	254 (37.4)	97 (36.6)	0.8 (0.6–1.2)[c]

Abbreviations: *OR* odds ratio, *CI* confidence interval

[a] Values do not add up to total ($n = 712$) due to the exclusion of women answering "Does not apply to me"

[b] Adjusted for education and severity of NVP

[c] Adjusted for age, education and severity of NVP

Italic effect estimates indicate significant findings

severe symptoms without pharmacological treatment, and many women had been on sick leave due to NVP without concomitant use of medicines. Moreover, our findings indicate that treatment guidelines are not consistently followed.

As expected, meclizine was the most commonly used medicine for NVP. Antihistamines are considered first-line treatment in Norway, in concordance with major international guidelines [8–15]. This is supported by reassuring results from a meta-analysis including close to 140,000 women finding that the use of antihistamines did not increase the risk of congenital malformations [35]. Only about half of the women in our study who had used only one medicine had used an antihistamine, which may indicate that treatment guidelines which generally recommend antihistamines as first choice are not followed for the other half. The choice of treatment is based on the individual risk-benefit assessment together with the clinical judgement which may explain this finding. Metoclopramide was the second most commonly used medicine for NVP, with surprisingly almost as many users as meclizine. This could be due to the majority of the responders having moderate to severe symptoms. Major guidelines for the treatment of NVP recommend the use of a dopamine antagonist, if symptoms are not sufficiently managed by antihistamines [8, 9, 11, 14, 15]. Results from large observational studies including more than 3000 and 28,000 women found no increased risk of congenital birth defects among women who had used metoclopramide [36, 37] and support the use. However, in June 2013, the European Medicines Agency (EMA) recommended that metoclopramide should be used for a maximum of five days, with the maximum dose of 10 mg up to three times daily, due to efforts to reduce the risk of neurological side effects [38]. Among women being pregnant at the time of participation, we found that 57 %, who had used metoclopramide, used it for more than 1 week. Women being pregnant at the time of participation, who used metoclopramide, must have used it after the EMA warning was issued. Our finding may indicate that the EMA warning is not generally known or accepted among GPs in Norway or that individual risk-benefit assessments have been performed and found to justify use. Of note, extrapyramidal side effects are also listed as adverse effects of prochlorperazine and chlorpromazine [39, 40], so the use of metoclopramide may be due to the lack of other perceived safe alternatives. Additionally, it should be noted that the U.S. Food and Drug Administration (FDA) recommends restricting use of metoclopramide to a maximum of 12 weeks [41].

Treatment with either meclizine or metoclopramide was most often initiated by a general practitioner, while ondansetron most often was initiated by a gynaecologist or a hospital physician. Ondansetron is listed as third-line therapy in several guidelines and is recommended for patients with more severe symptoms [9, 14, 15]. Women with severe symptoms are more likely to be referred to hospital, which may explain this finding. Indeed, women who had severe NVP as well as women who were hospitalised were significantly more likely to have used ondansetron. There have been discussions about the safety of ondansetron, especially when used during the first trimester [42–46]. The data from these studies do not suggest that ondansetron use is associated with a high risk of birth defects, but a slightly increased risk of cardiovascular malformations may exist [9]. Cases that are treated in hospital, however, are probably most often of such a severe nature that use of ondansetron is justified.

More women used CAM than conventional medicines (54 vs. 39 %). This is in accordance with recommendations in guidelines of managing the symptoms with conservative approaches (such as dietary and lifestyle changes, ginger, acupressure and/or acupuncture) firstly before considering any pharmacological treatment. The high prevalence of CAM use is in accordance with that reported by Hollyer et al. of 61.2 % [47]. Many women who used CAM also used conventional medicines. Consequently, the use of CAM did not seem to exclude the use of conventional medicines. The most commonly used CAM in this study was ginger. Ginger has been reported to be commonly used for NVP [47–50] and has been shown to be more effective than placebo and equally effective as vitamin B6 and dimenhydrinate for NVP [51]. No increased risk of malformations, stillbirth/perinatal death, low birth weight, preterm birth or low Apgar score were found in a cohort study with 1020 ginger-exposed pregnancies (466 in the first trimester) [52]. Acupressure was the second most commonly used CAM, close to ginger, followed by acupuncture. Ginger, acupressure and/or acupuncture are mentioned in national and major guidelines for the treatment of NVP [9, 10, 12]. Vitamin B6 is also recommended in guidelines, but was used by relatively few women in this study.

The majority of women using any of the CAM listed in Table 3 initiated the treatment themselves, not on recommendations of a health care provider. Of note, the treatment most often initiated by midwives was acupuncture. These results are in accordance with previous findings [48, 49, 53].

The severity of nausea was strongly associated with the use of all types of treatments, which are in line with previous findings [21, 47, 54], and may reflect the distress caused by more severe symptoms. Severe NVP symptoms have been associated with severe morbidity and shown to have major impact on the women's lives [6, 19–24], implying that the reduction of the intensity of severe symptoms should be of high priority.

Compared to women with a bachelor degree, fewer women with a master degree used medicines for NVP. Education and working status have previously been identified as factors associated with the use of medicines among women with NVP [27, 55, 56]; however, our findings are somewhat contrasting the previous findings, indicating that no firm conclusion may be drawn.

Among women who had been on sick leave due to NVP, 62 % of the women were given sick leave without concomitant medical treatment and 47 % did not use any medicine for NVP at any time during the pregnancy. A need for sick leave due to NVP indicates symptoms of such severity that they interfere with daily life functioning and consequently indicate a need for medical treatment [8, 11, 57, 58]. Although it is not likely that medical treatment would enable all women to work full time, medical treatment may alleviate the symptoms to such a degree that would enable some of the women to work at least part time. NVP has been found to be the third most common reason for sick leave in Norway during pregnancy [59] and has high socioeconomic consequences. Furthermore, one third of the women with severe NVP (PUQE score ≥ 13) did not use any medicines for NVP. Women with more severe symptoms are at risk for hospitalisation due to dehydration and electrolyte disturbances [28].

The majority of the women reported the onset of symptoms in or before pregnancy week 10. The onset after this week is seldom seen in nausea and vomiting of pregnancy and may be due to other causes [57]. Consequently, we believe that the 17 women who reported the onset after this week may suffer from a differential diagnosis rather than NVP.

The findings in this Norwegian study revealed that women's beliefs about medicines had an important impact on their use for NVP. These findings are in accordance to the previous findings by Nordeng et al. [31], indicating that women with NVP largely share the attitudes of pregnant women in general. Interestingly, in our study, the severity of symptoms was associated with women's attitudes. Though, a large proportion of the women with severe symptoms agreed to having a higher threshold for the use of medicines while pregnant (77 %), we found a decreasing degree of agreement with increasing degree of severity of NVP. Likewise, fewer women with severe NVP agreed with statement S4 "I refrain from using medicines despite having NVP, just in case", the more severe the symptoms were. This may illustrate 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. The fact that 61 % of the women with severe symptoms who had used medicines for NVP agreed that they used less medicines than needed is disturbing, especially because there are well defined treatment guidelines describing possible treatment options [9, 14, 15]. Together with the finding that 78 % of the women who used medicines were anxious of how the medicines affected their foetus, this illustrates a need for comprehensive and reassuring information about treatment options to subdue the women's anxiety and insecurity which are likely to negatively impact their adherence [60]. Counselling and proper risk communication may temper women's negative beliefs about medicines and increase adherence during pregnancy [61, 62].

Strengths and limitations

Our study has several limitations that need to be taken into consideration when interpreting our results. First, women suffering from severe symptoms may be more motivated to participate in the study and could thereby explain the high prevalence of women with severe symptoms in our study population. On the other hand, the most severely affected women will be too sick to participate. Moreover, maternal reporting of information was retrospective for women not being at the peak of their NVP symptoms, introducing a risk for overestimating the severity of NVP symptoms. Koren et al. have previously demonstrated that women have a tendency to overestimate the symptoms when reporting retrospectively [63]. We tried to reduce this risk by excluding all women with a youngest child older than 1 year of age, however, we cannot rule out this risk completely. Another study that used the three PUQE questions to assess NVP retrospectively did not find evidence of differential recall when stratified on gestational age [64]. Of note, the classification of severity of NVP was based on the PUQE score. It is important to remember that not all aspects that contribute to the overall experience of the severity of NVP are measured by PUQE; hence, different women with moderate NVP as classified by PUQE may differ in the experience of the impact of their symptoms.

Second, a conventional response rate could not be calculated and a selection bias of the target population cannot be ruled out due to the use of a Web-based questionnaire. However, this approach enabled us to reach a high number of women from all over Norway, resulting in a sample with a geographic spread strikingly similar with that of the general birthing population (Appendix 1) [33, 34]. Moreover, as some antihistamines are available as over-the-counter (OTC) medicine, and the severity of NVP is not recorded in the prescription database unless diagnosed as HG, determining the prevalence rate of treatment according to severity is problematic, excluding a registry-based approach. The Internet is increasingly used for research purposes [65], and recruitment via the Internet has shown reasonable validity in epidemiological studies [66, 67]. The information reported in Web-based questionnaires has been found to be of equal quality, equivalent to and as reliable as the information provided on paper in studies from different research fields [68–70]. Moreover, as the Internet penetration rate is very high in Norway (97 % of the women aged 16–44 years use Internet on daily basis) [71], this methodology may be especially appropriate for women in reproductive age. Furthermore, the women who participated in the study were reasonably comparable to the general birthing population of Norway. Of note, women in this study generally had a higher level of education compared to the general birthing population. The results should be interpreted with these limitations in mind.

Studies to determine the benefit of early treatment of NVP are warranted. Furthermore, future work is needed to determine the safety of commonly used medications for NVP such as metoclopramide (risk of neurological side effects) and ondansetron (cardiovascular complications). Studies addressing the attitudes among health care personnel involved in treatment of NVP and patients' adherence to NVP treatment are warranted.

Conclusion

A large proportion of women suffered from moderate to severe symptoms of NVP, many of whom did not receive any pharmacological treatment. Though antihistamines were the most commonly used medicines for NVP, closely followed by metoclopramide, our findings indicate that treatment guidelines are not consistently followed. Many women, who had been on sick leave due to NVP, were not prescribed medicines beforehand or at the same time as the sick leave certificate was issued. Future studies should investigate whether earlier identification and treatment of NVP can reduce sick leave and hospitalisation due to this condition in pregnancy.

Acknowledgments We thank the providers of the websites for contributions in the recruitment phase, and all the women who participated in the study. KH received funding for her PhD project from The Norwegian Research Council (Grant no. 195475).

Author's contribution KH, LH, GCH and HN conceived and designed the study. AS collected the data. KH performed the statistical analyses and drafted the manuscript. All authors contributed to the interpretation of the results and to the final manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Einarson TR, Piwko C, Koren G (2013) Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol 20(2):e171–183
2. Gadsby R, Barnie-Adshead AM, Jagger C (1993) A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 43(371):245–248
3. Lacroix R, Eason E, Melzack R (2000) Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 182(4):931–937
4. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG (1985) Epidemiology of vomiting in early pregnancy. Obstet Gynecol 66(5):612–616
5. Vellacott ID, Cooke EJ, James CE (1988) Nausea and vomiting in early pregnancy. Int J Gynaecol Obstet 27(1):57–62
6. Eliakim R, Abulafia O, Sherer DM (2000) Hyperemesis gravidarum: a current review. Am J Perinatol 17(4):207–218. doi:10.1055/s-2000-9424
7. Vandraas K, Vikanes Å, Vangen S, Magnus P, Støer N, Grjibovski A (2013) Hyperemesis gravidarum and birth outcomes—a population-based cohort study of 2.2 million births in the Norwegian Birth Registry. BJOG 120(13):1654–1660
8. Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, Martel MJ, Sprague AE, Wilson AK (2002) The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can 24(10):817–831, quiz 832–813
9. Smith J, Refuerzo J, Ramin S (2014) Treatment and outcome of nausea and vomiting of pregnancy. UpToDate
10. National Collaborating Centre for Women's and Children's Health (2008) Antenatal care: routine care for the healthy pregnant woman. National Institute for Health and Clinical Excellence (NICE). http://www.nice.org.uk/guidance/cg62/evidence/full-guideline-corrected-june-2008-196748317. Accessed 19 March 2015
11. ACOG (American College of Obstetrics and Gynecology) (2015) Practice bulletin No. 153, nausea and vomiting of pregnancy. Obstet Gynecol 126(3):e12–24. doi:10.1097/01.AOG.0000471178.18186.d6
12. Sosial og helsedirektoratet [The Norwegian Directorate of Health and Social Affairs] (2005) Nasjonale faglige retningslinjer: Retningslinjer for svangerskapsomsorgen [A National Clinical Guideline for antenatal care]. 2005 edn
13. Norsk Legemiddelhåndbok [Norwegian Medicines Handbook] (2015) http://legemiddelhandboka.no/Terapi/søker/+%2Bsvangerskapskvalme/19493. Accessed 09 April 2015
14. Norsk gynekologisk forening [The Norwegian Society of Obstetrics and Gynecology] (2014) Veileder i fødselshjelp [Obstetric guidelines issued by The Norwegian Society of Obstetrics and Gynaecology (NGF)]
15. BMJ Best Practice (2015) Nausea and vomiting in pregnancy. http://bestpractice.bmj.com/best-practice/monograph/999.html
16. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G (2000) Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 62(6):385–392. doi:10.1002/1096-9926(200012)62:6<385::Aid-Tera5>3.0.Co;2-Z
17. Locock L, Alexander J, Rozmovits L (2008) Women's responses to nausea and vomiting in pregnancy. Midwifery 24(2):143–152. doi:10.1016/j.midw.2006.12.001
18. Munch S (2000) A qualitative analysis of physician humanism: women's experiences with hyperemesis gravidarum. J Perinatol 20(8 Pt 1):540–547
19. Smith C, Crowther C, Beilby J, Dandeaux J (2000) The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol 40(4):397–401
20. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, Torrance GW (2002) The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol 186(5 Suppl Understanding):S220–227
21. Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA (2000) Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol 21(3):129–136

22. Lacasse A, Rey E, Ferreira E, Morin C, Berard A (2008) Nausea and vomiting of pregnancy: what about quality of life? BJOG 115(12):1484–1493. doi:10.1111/j.1471-0528.2008.01891.x
23. Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM (2008) The psychosocial burden of hyperemesis gravidarum. J Perinatol 28(3):176–181. doi:10.1038/sj.jp.7211906
24. Mazzotta P, Stewart DE, Koren G, Magee LA (2001) Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol 22(1):7–12
25. The Norwegian Welfare and Labour Administration (2011) Sickness benefits for employees. The Norwegian Welfare and Labour Administration. https://www.nav.no/en/Home/Benefits+and+services/Relatert+informasjon/Sickness+benefits+for+employees.283831.cms. Accessed 19 Aug 2015
26. The Norwegian Directorate of Health (2014) Svangerskapskontroller [pregnancy consultations]. helsenorge.no. https://helsenorge.no/gravid/svangerskapskontroller. Accessed 27 Aug 2015
27. 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 Childbirth 15(1):321
28. Ebrahimi N, Maltepe C, Bournissen FG, Koren G (2009) Nausea and vomiting of pregnancy: using the 24-hour pregnancy-unique quantification of emesis (PUQE-24) scale. J Obstet Gynaecol Can 31(9):803–807
29. Koren G, Piwko C, Ahn E, Boskovic R, Maltepe C, Einarson A, Navioz Y, Ungar WJ (2005) Validation studies of the pregnancy unique-quantification of emesis (PUQE) scores. J Obstet Gynaecol 25(3):241–244. doi:10.1080/01443610500060651
30. Birkeland E, Stokke G, Tangvik RJ, Torkildsen EA, Boateng J, Wollen AL, Albrechtsen S, Flaatten H, Trovik J (2015) 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 10(4):e0119962
31. Nordeng H, Koren G, Einarson A (2010) Pregnant women's beliefs about medications—a study among 866 Norwegian women. Ann Pharmacother 44(9):1478–1484. doi:10.1345/aph.1P231
32. Lupattelli A, Spigset O, Twigg M, Zagorodnikova K, Mårdby A, Moretti M, Drozd M, Panchaud A, Hämeen-Anttila K, Rieutord A (2014) Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open 4(2):e004365
33. Medical Birth Registry of Norway - Statistics (2015) http://mfr-nesstar.uib.no/mfr/. Accessed 08 July 2015
34. StatBank Norway, Table 08921: Persons 16 years and older, by sex, age and level of education. Numbers and per cent (C) (2015) Statistics Norway. https://www.ssb.no/en/statistikkbanken. Accessed 08 July 2015
35. Chin J, Gregor S, Persaud N (2014) Re-analysis of safety data supporting doxylamine use for nausea and vomiting of pregnancy. Am J Perinatol 31(8):701–710
36. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Melbye M, Hviid A (2013) Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. JAMA 310(15):1601–1611. doi:10.1001/jama.2013.278343
37. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A (2009) The safety of metoclopramide use in the first trimester of pregnancy. New Engl J Med 360(24):2528–2535
38. European Medicines Agency (2013) European Medicines Agency recommends changes to the use of metoclopramide. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146614.pdf. Accessed 19 March 2015
39. Summary of product characteristics - Stemetil 5 mg tablets (2014) The Norwegian Medicines Agency. http://www.legemiddelverket.no/_layouts/Preparatomtaler/Spc/0000-03629.pdf?id=25072014142813. Accessed 1 Oct 2015
40. Summary of product characteristics - Chlorpromazine 50 mg tablets (2014) The electronic medicines compendium (eMC). http://www.medicines.org.uk/emc/medicine/29499. Accessed 1 Oct 2015
41. FDA (2010) Safety information - Reglan (metoclopramide) tablets, ODT (Orally disintegrating tablets), and injection. FDA. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm. Accessed 08 July 2015
42. Koren G (2014) Scary science: ondansetron safety in pregnancy-Two opposing results from the same Danish registry. Ther Drug Monit. doi:10.1097/FTD.0000000000000020
43. Andersen JT, Jimenez-Solem E, Andersen NL, Poulsen HE (2013) Abstract 25, pregnancy session 1. Ondansetron use in early pregnancy and the risk of congenital malformations – a register based nationwide cohort study. International Society of Pharmaco-Epidemiology, Montreal
44. Pasternak B, Svanstrom H, Hviid A (2013) Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med 368(9):814–823. doi:10.1056/NEJMoa1211035
45. Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, National Birth Defects Prevention S (2012) Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defect Res Part A Clin Mol Teratol 94(1):22–30. doi:10.1002/bdra.22865
46. Danielsson B, Wikner BN, Källén B (2014) Use of ondansetron during pregnancy and congenital malformations in the infant. Reprod Toxicol 50:134–137
47. Hollyer T, Boon H, Georgousis A, Smith M, Einarson A (2002) The use of CAM by women suffering from nausea and vomiting during pregnancy. BMC Complement Altern Med 2:5
48. Holst L, Wright D, Haavik S, Nordeng H (2009) The use and the user of herbal remedies during pregnancy. J Altern Complement Med 15(7):787–792. doi:10.1089/acm.2008.0467
49. Nordeng H, Havnen GC (2004) Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiol Drug Saf 13(6):371–380. doi:10.1002/pds.945
50. Nordeng H, Bayne K, Havnen GC, Paulsen BS (2011) 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 17(3):147–151. doi:10.1016/j.ctcp.2010.09.002
51. Dante G, Pedrielli G, Annessi E, Facchinetti F (2013) Herb remedies during pregnancy: a systematic review of controlled clinical trials. J Matern Fetal Neonatal Med 26(3):306–312. doi:10.3109/14767058.2012.722732
52. Heitmann K, Nordeng H, Holst L (2013) Safety of ginger use in pregnancy: results from a large population-based cohort study. Eur J Clin Pharmacol 69(2):269–277. doi:10.1007/s00228-012-1331-5
53. Wills G, Forster D (2008) Nausea and vomiting in pregnancy: what advice do midwives give? Midwifery 24(4):390–398. doi:10.1016/j.midw.2007.05.002
54. Kramer J, Bowen A, Stewart N, Muhajarine N (2013) Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. MCN Am J Matern Child Nurs 38(1):21–27. doi:10.1097/NMC.0b013e3182748489
55. Asker C, Norstedt Wikner B, Kallen B (2005) Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol 61(12):899–906. doi:10.1007/s00228-005-0055-1
56. Markl GE, Strunz-Lehner C, Egen-Lappe V, Hasford J (2007) Prescribing patterns of anti-emetic drugs during pregnancy in Germany. Arch Gynecol Obstet 275(6):461–467

57. Maltepe C, Koren G (2013) The management of nausea and vomiting of pregnancy and hyperemesis gravidarum—a 2013 update. J Popul Ther Clin Pharmacol 20(2):e184–192
58. Gadsby R, Barnie-Adshead AM (2011) Severe nausea and vomiting of pregnancy: should it be treated with appropriate pharmacotherapy? Obstet Gynaecol 13:107–111
59. Dorheim S, Bjorvatn B, Eberhard-Gran M (2013) Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. BJOG 120(5):521–530
60. Lupattelli A, Spigset O, Nordeng H (2014) Adherence to medication for chronic disorders during pregnancy: results from a multinational study. Int J Clin Pharm 36(1):145–153. doi:10.1007/s11096-013-9864-y
61. Jasper JD, Goel R, Einarson A, Gallo M, Koren G (2001) Effects of framing on teratogenic risk perception in pregnant women. Lancet 358(9289):1237–1238
62. Einarson A, Selby P, Koren G (2001) Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counselling. J Psychiatry Neurosci 26(1):44–48
63. Koren G, Maltepe C, Navioz Y, Wolpin J (2004) Recall bias of the symptoms of nausea and vomiting of pregnancy. Am J Obstet Gynecol 190(2):485–488. doi:10.1016/j.ajog.2003.08.039
64. Lacasse A, Rey E, Ferreira E, Morin C, Berard A (2009) Epidemiology of nausea and vomiting of pregnancy: prevalence, severity, determinants, and the importance of race/ethnicity. BMC Pregnancy Childbirth 9:26. doi:10.1186/1471-2393-9-26
65. Eysenbach G (2004) Improving the quality of web surveys: the checklist for reporting results of internet E-surveys (CHERRIES). J Med Internet Res 6(3):e34. doi:10.2196/jmir.6.3.e34
66. van Gelder MM, Bretveld RW, Roeleveld N (2010) Web-based questionnaires: the future in epidemiology? Am J Epidemiol 172(11):1292–1298. doi:10.1093/aje/kwq291
67. Ekman A, Dickman PW, Klint A, Weiderpass E, Litton JE (2006) Feasibility of using web-based questionnaires in large population-based epidemiological studies. Eur J Epidemiol 21(2):103–111. doi:10.1007/s10654-005-6030-4
68. Whitehead L (2011) Methodological issues in Internet-mediated research: a randomized comparison of internet versus mailed questionnaires. J Med Internet Res 13(4):e109. doi:10.2196/jmir.1593
69. Ritter P, Lorig K, Laurent D, Matthews K (2004) Internet versus mailed questionnaires: a randomized comparison. J Med Internet Res 6(3):e29. doi:10.2196/jmir.6.3.e29
70. Touvier M, Mejean C, Kesse-Guyot E, Pollet C, Malon A, Castetbon K, Hercberg S (2010) Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. Eur J Epidemiol 25(5):287–296. doi:10.1007/s10654-010-9433-9
71. Norwegian media barometer - Table: 04519: percentage internet users and minutes used for internet an average day, by sex and education (2015) Statistics Norway https://www.ssb.no/statistikkbanken/selecttable/hovedtabellHjem.asp?KortNavnWeb=medie&CMSSubjectArea=kultur-og-fritid&PLanguage=1&checked=true. Accessed 08 July 2015