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ORIGINAL ARTICLE

Ondansetron use in nausea and vomiting during pregnancy: A descriptive analysis of prescription patterns and patient characteristics in UK general practice

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Aims: The objective of this study was to describe ondansetron drug utilization patterns during pregnancy to treat nausea and vomiting in pregnancy (NVP). Moreover, we aimed to describe the maternal factors associated with NVP and antiemetic use.

Methods: The data consist of pregnancies with a live birth(s) within an IMRD-UK registered GP practice. Descriptive statistics were used to investigate patterns of ondansetron use in pregnancy and to describe maternal characteristics associated with NVP and antiemetic drug utilization. We differentiate first- from second-line use during pregnancy using antiemetic prescription pathways.

Results: The dataset included 733 633 recorded complete pregnancies from 2005 to 2019. NVP diagnosis and ondansetron prescription prevalence increased from 2.7% and 0.1% in 2005 to 4.8% and 2.5% in 2019 respectively. Over the period 2015–2019, the most common oral daily dosages were 4 mg/d (8.5%), 8 mg/d (37.1%), 12 mg/d (37.5%) and between 16 and 24 mg/d (16.9%). Prescription of ondansetron was initiated during the first trimester of pregnancy in 40% of the cases and was moderately used as a first-line therapy (2.8%), but preferred choice of second-line therapy. Women with mental health disorders, asthma and/or prescribed folic acid were more likely to experience NVP and use antiemetics in pregnancy than their counterparts.

Conclusion: This study confirms that ondansetron is increasingly used off-label to treat NVP during pregnancy, also in the first trimester and before other prescription antiemetics have been prescribed. Several maternal comorbidities and folic acid use were more common among women experiencing NVP and using antiemetics, including ondansetron.

KEYWORDS
antiemetics, hyperemesis gravidarum, IMRD-UK, nausea and vomiting in pregnancy, ondansetron

1 | INTRODUCTION

Nausea and vomiting affects up to 80% of pregnant women worldwide and is the most common medical condition in pregnancy.[1] The symptoms of nausea and vomiting of pregnancy (NVP) vary in severity ranging from mild to a life-threatening condition. Hyperemesis gravidarum (HG) is among the latter, affecting 1% of the pregnant population[2] and is characterized by persistent nausea and vomiting, dehydration, electrolyte and nutritional imbalances, and excessive weight loss. HG is the most common reason for hospitalization during the first part of pregnancy[3] and is associated with an increased risk of preterm birth.[4]

NVP usually manifests between 4 and 7 weeks of pregnancy, with the peak severity of hyperemesis occurring at around 11 weeks with 90% of NVP cases resolved by 20 weeks' pregnancy. Treatment of NVP is recommended when it impacts on daily life and functioning and if there is an increased risk of developing HG. The majority of clinical treatment guidelines recommend lifestyle and dietary changes as first-line management[5,6] and if symptoms are severe or persist, pharmacological therapy is recommended, but universal national guidelines for treatment of NVP are lacking.[7]

Ondansetron is a selective 5-HT3-receptor antagonist and is currently licensed in the EU for the management of nausea and vomiting associated with cytotoxic chemotherapy and radiation (adults and children aged >6 mo) and for the prevention or treatment of postoperative nausea and vomiting (adults and children aged >1 mo).[7] Over recent years, it is increasingly used off-label in European countries as a treatment for severe NVP and to prevent progression to HG.[8]

In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) guidance, last updated June 2016, recommend ondansetron as a second-line treatment for NVP.[9] This RCOG NVP guidance recommends that the use of ondansetron should be limited to patients who are not adequately managed with alternative treatments and preferably used after the first trimester of pregnancy. The main recommendations do not concentrate on the absolute timing of exposure but rather on the prioritization of alternative treatments. The executive summary of recommendations includes a statement saying that there is evidence that ondansetron is safe and effective, but because data are limited it should be used as second-line therapy.

In the UK, the proportion of pregnancies with an ondansetron prescription during pregnancy rose from 0.25% in 2013 to approximately 1% in 2017.[10] In the USA, ondansetron is 1 of the 8 drugs currently recommended by the 2018 clinical guidelines from the American College of Gynecology for the treatment of NVP.[11] In 2014, it was the most common treatment for NVP in the US (25% of all pregnancies).[12] Most clinical guidelines recommend reserving use of ondansetron for severe NVP, if other treatments have failed to provide sufficient NVP symptom relief and delaying use until after 10 weeks' gestation.[13]

Studies have questioned the safety of ondansetron use in the first trimester of pregnancy.[14–16] Two large studies from the USA[17,18] have been published with conflicting results related to the risks of in utero exposure to ondansetron and various birth defects. Zambelli-Weiner and colleagues examined 864 083 mother–baby pairs of whom 73 471 (8.5%) had prescriptions for ondansetron during the first trimester. First trimester exposure to ondansetron was associated with an increased risk of cardiac defects (adjusted odds ratio [OR]: 1.52, 95% confidence interval [CI]: 1.35–1.70) and with a nonsignificant tendency to orofacial cleft defects (OR: 1.32, 95% CI 0.76–2.28). Huybrechts and colleagues examined 1 816 414 pregnancies of which 88 467 (4.9%) were exposed in the first trimester. They found an increased risk of oral clefts (adjusted relative risk [RR] 1.24, 95% CI 1.03–1.48; 3 additional cases per 10 000 women treated with ondansetron in the first trimester) but not cardiac defects (RR: 0.99, 95% CI 0.93–1.06).

After reviewing the available literature, the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) recommended in July 2019 that the Marketing Authorisation Holders of ondansetron-containing medicinal products should update the summary of product characteristics indicating that ondansetron should not be used during the first trimester of pregnancy due to a potential small increased risk of oral clefts and conflicting findings on cardiac defects.[19]

Given the debate and increasing ondansetron use, the aim of this study was to characterize the utilization patterns of antiemetics in

What is already known about this subject

- In the UK, The Royal College of Obstetricians and Gynaecologists guidance recommends use of ondansetron as a second-line medication for nausea and vomiting in pregnancy (NVP).
- Published research has suggested that ondansetron may be associated with a small increased risk of birth defects, including oral clefts.
- Prior studies report prevalence of antiemetic use in pregnancy at between 5.5 and 12.9% in other European countries, with prevalence of ondansetron exceeding 25% in the USA.

What this study adds

- Rates of severe NVP in the UK increased from 2.7% in 2005 to 4.8% in 2019.
- Rates of ondansetron prescriptions in pregnancy increased in the UK from 0.01% in 2005 to 2.5% in 2019.
- 40.0% of ondansetron exposure was initiated in the first trimester of pregnancy between 2015 and 2019.
- Ondansetron was the preferred second line on prescription treatment for NVP in the UK between 2015 and 2019 with only limited use as first-line on prescription treatment (2.8%).
- Maternal factors associated with NVP and antiemetic use were prescribed folic acid, asthma and mental health disorders.

general, and ondansetron in specific for the treatment of NVP in a UK general practice data base. This included differentiating first-line use of ondansetron from second-line use using antiemetic prescription pathways. In addition, we aimed to describe characteristics of women who were more likely to experience NVP and require antiemetic treatment. The overall aim of the study is to contribute to the debate regarding pharmacological management of NVP. As clinical treatment guidelines for NVP exist in countries other than the UK,[11] the results may stimulate future studies in the wider European population as well as the establishment of international NVP guidelines.

2 | METHODS

2.1 | Data sources

Our study was based on data from General Practitioners (GPs) across the UK recorded in the IQVIA Medical Research Data (IMRD)-UK (formerly known as THIN), release January 2020.[20] The data have been collected since 1987, covering about 6% of the UK population, and are broadly generalizable to the whole UK population in terms of age, deprivation and geographic distribution and linked via an anonymous patient ID number allowing patients to be followed longitudinally over time. Data on diagnoses are recorded as Read codes, a hierarchical classification system,[21] and prescriptions are mapped to ATC codes.

2.2 | Study cohort

The study period for this analysis ranged from 1 January 2005 to 31 December 2019. The study population consists of pregnancies with a live birth within an IMRD-UK registered GP practice. Matching was done as follows; all births in the dataset were clustered to identify multiple births and were then attached to potential mothers by matching them with mothers with the same family number and practice number and refining the match on the basis of clinical details that have a credible temporal relationship to the birth (See Appendices for further information).

2.3 | Indication

NVP was identified using clinical Read codes and classified as severe NVP/HG or mild/moderate NVP as listed in Tables A1 and A2. In total, 17 severe NVP/HG codes and 11 mild/moderate code were used. These NVP codes were utilized to identify medications used as off- label antiemetics.

2.4 | Exposure

The primary focus of this study is exposure to ondansetron during a pregnancy. Table A3 provides the product codes for ondansetron in IMRD-UK. For this study we adopted the categorization of first-, second- and third-line treatments as recommendations by the Royal College of Obstetricians and Gynaecologists for the treatment of NVP and HG (Table 1) based on a treatment algorithm for NVP and HG as identified in Appendix IV in the RCOG Guidelines.[9] First-line treatments included cyclizine, prochlorperazine, promethazine and/or chlorpromazine. In addition to ondansetron, second-line treatments included metoclopramide and/or domperidone. Third-line prescriptions are reserved for hospitals and out of scope in this analysis.

First-line usage is defined when first prescription of ondansetron within the pregnancy occurs without prior prescription of any other antiemetic within the same pregnancy. Second-line usage occurs when the first prescription of ondansetron within a pregnancy is preceded by a prescription of another antiemetic.

TABLE 1 Royal College of Obstetricians and Gynaecologists Green-top Guideline No 69 (3)[a]

First-line treatment of NVP
• Cyclizine 50 mg PO, IM or IV 8 hourly • Prochlorperazine 5–10 mg 6–8 hourly PO; 12.5 mg 8 hourly IM/IV; 25 mg PR daily • Promethazine 12.5–25 mg 4–8 hourly PO, IM, IV or PR • Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR
Second-line treatment of NVP
• Metoclopramide 5–10 mg 8 hourly PO, IV or IM (maximum 5 days duration) • Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR • Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV
Third-line treatment of NVP
• Corticosteroids: Hydrocortisone 100 mg twice daily IV and once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached

IM = intramuscular; IV = intravenous; PO = by mouth; PR = by rectum.
[a]Royal College of Obstetricians & Gynaecologists. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum. Green-top guidelines no 69; 2016.

2.5 | Exposure time frames

Exposure to antiemetics was defined as the presence of at least 1 prescription of the medications selected within each time frame. Time frames of interest included the entire pregnancy, pregnancy trimesters (trimester 1: 1–90 d after last menstrual period [LMP]; trimester 2: 91–180 d after LMP; trimester 3: >180 d after LMP).

2.6 | Covariates

Covariates to assess the characteristics of women with and without antiemetic medication prescription fillings during pregnancy included sociodemographic characteristics, comorbidities and comedications.

Sociodemographic characteristics included maternal age at delivery, body mass index, weight and height, sex of child, multiple births, smoking in pregnancy and prior folic acid. Comorbidities included psychosis, anxiety, asthma, depression, diabetes, eating disorder, epilepsy, hypothyroid, personality disorder. Folate is widely used in the UK from before conception to 12th week of pregnancy but will be supplied in most cases in low-dose form without prescription.

2.7 | Statistical analyses

Descriptive statistics were used to present births and severity of nausea and vomiting recorded during pregnancy and total number of pregnancies exposed to ondansetron over the period 2005–2019.

Mean observed daily doses were calculated for those prescriptions with known daily dose of solid ondansetron over the period 2015–2019 and compared with physician recommended daily dose. For most prescriptions, the prescribed quantity divided by the interval to the subsequent prescription was used as an estimate for daily dose.

Exposure time for each pregnancy was calculated based on the total amount of prescriptions during the pregnancy divided by the estimated daily dosage. For women with >1 prescription, their first exposure would be used in the calculation of the proportion of ondansetron prescriptions in the first trimester.

To evaluate whether treatment guidelines were followed to treat NVP, we assessed to which degree a first-line antiemetic had been prescribed prior to an ondansetron prescription for the treatment of NVP. We visualized this through prescription pathways (river plot). According to guidelines,[12] ondansetron should be reserved as a second-line treatment, thus we assessed the proportion of the first prescription of ondansetron being preceded by a prescription of a first-line antiemetic therapy (cyclizine, prochlorperazine, promethazine, chlorpromazine) through prescription pathways. In particular, this examined if products other than those nominated as first-line in this study were perceived as first-line in clinical practice. In this analyses, we restricted the analyses to pregnancies with at least 1 ondansetron prescription in pregnancy.

To characterize mothers with NVP, socio-demographic characteristics, comedication and comorbidities were further broken down and described (count, mean and standard deviation of continuous variables and proportion of categorical variables) for women with and without nausea.

Finally, we examined the presence of other underlying comorbidities potentially leading to nausea, and consequent exposure to ondansetron, in pregnancies through exposure to other medications (using ATC codes). We also looked at a period before pregnancy (7 to 1 mo before LMP) in order to see what changed when the woman became pregnant. The calculation is restricted to women whose clinical record extends from at least 213 days before the LMP date. All pregnancies with any prescription were included.

The statistical analyses were performed with SAS v9.4.

2.8 | Ethical permission

IMRD incorporates data from THIN, A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.

2.9 | Public and patient involvement

This study was endorsed by the EMA PRAC committee, which consists of patient and healthcare professional representatives.

3 | RESULTS

The study included 733 633 recorded pregnancies between 1 January 2005 and 31 December 2019. From 2005 to 2019 there was a steady increase in recorded NVP diagnosis in pregnancies from 3.6% in 2005 to 6.0% in 2019. Rates of severe NVP/HG almost doubled from 2.7% in 2005 to 4.8% in 2019 (Figure 1).

The prevalence of ondansetron prescription during pregnancies increased from 0.1% in 2005 to 2.5% in 2019 (Figure 2).

3.1 | Ondansetron formulations and daily dosages

The main administration form of ondansetron prescription between 2015–2019 (n = 12 712) was oral solid tablets (92.9%), followed by

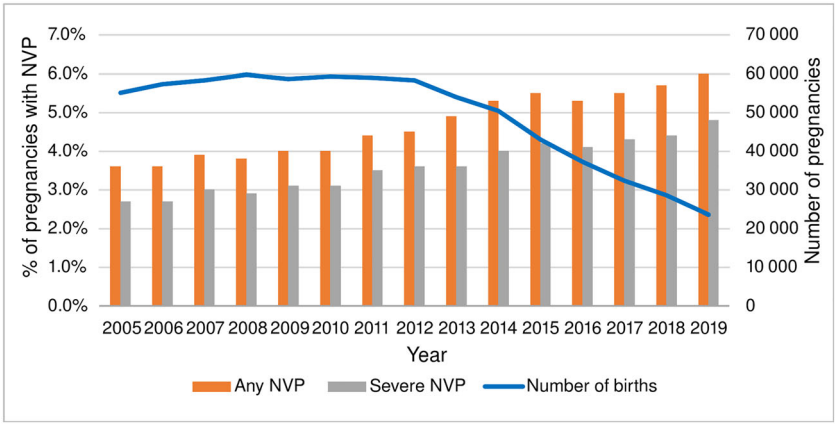

FIGURE 1 Percentage of women experiencing any or severe nausea and vomiting (NVP) during pregnancies, 2005–2019, IMRD-UK. The reduction in births by time in IMRD-UK can be attributed to the reduction in active patients in the database, especially those coming from English practices

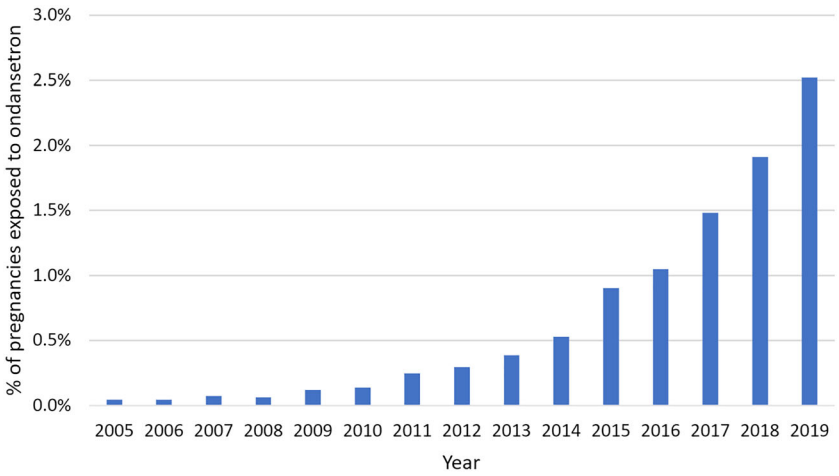

FIGURE 2 Percentage of pregnancies (that result in live births) exposed to ondansetron, 2005–2019, IMRD-UK.

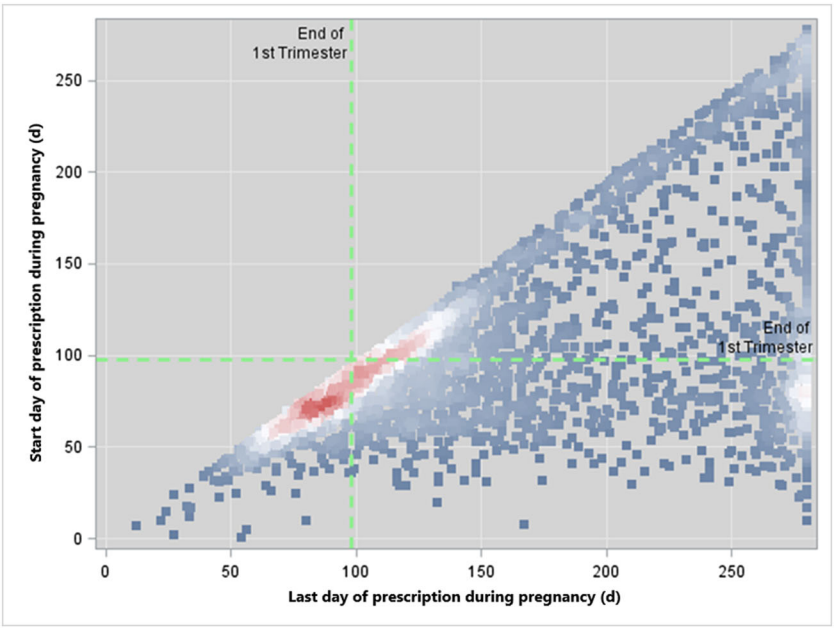

FIGURE 3 Start and end of ondansetron treatment episodes (calculated using the estimated daily dose and the prescribed quantities) in days from LMP, 2015–2019, IMRD-UK. Each point represents an episode of exposure to ondansetron in pregnancy. The colours indicate the density of points, red is the highest density and grey the lowest

oro-dispersible tablets (4.8%), suppositories (1.2%), oral liquids (1.1%) and injection (0.1%). For those prescriptions with known daily dosage of solid oral ondansetron (3871/12712;30.5%), 8.5% of the prescriptions were for 4 mg, 37.1% for 8 mg, 37.5% for 12 mg and 16.9% between 16 and 24 mg. The median prescribed daily dose of ondansetron tablets was 11.5 mg. The observed daily doses (median of 7.3 mg) were lower than the physician recommended daily doses (4–8 mg 6–8 hourly by mouth; 8 mg over 15 minutes 12 hourly intravenous).

3.2 | Trimesters of exposure

Exposure time was calculated for 2391 out of the 2401 ondansetron exposed pregnancies over the period 2015–1019. For 10 pregnancies, the exact total amount of exposures could not be established. In total, 957 (40.0%) initiated exposure during the first trimester. Figure 3 shows the pattern of exposure time in the first trimester. The most usual pattern is fairly short (<15 d) durations in the second half in the first trimester of the pregnancy as indicated by the red density spot in the figure. Some women might have > 1 episode of exposure during a pregnancy. In our study, 89.3% of the women had 1 exposure; 9.2% had 2 exposures; 1.2% had 3 exposures and 0.3% had 4 exposures.

3.3 | Order of ondansetron prescriptions

In Figure 4, prescription pathways show the trend in the use of ondansetron in comparison with other commonly used antiemetics during pregnancy and the order in which they are used. The populating included 164 942 pregnancies with at least 1 ondansetron prescription in pregnancy. This diagram shows that ondansetron is rarely

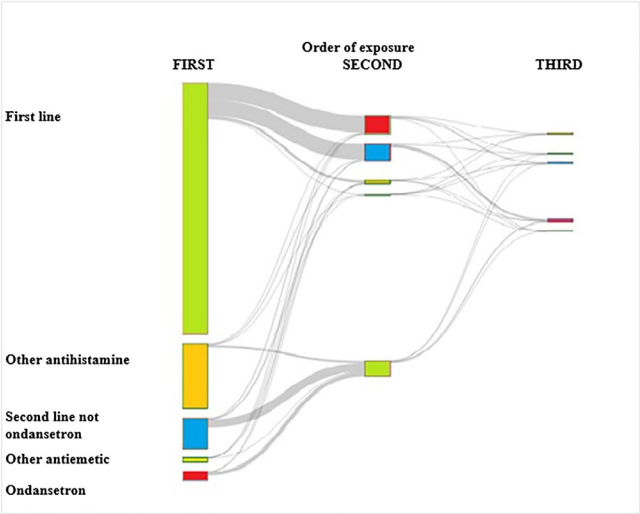

FIGURE 4 Diagram demonstrating the use of ondansetron as first- or second-line treatment in comparison with other treatments, 2015–2019, IMRD-UK. First line includes cyclizine, prochlorperazine, promethazine and chlorpromazine (69.3%), other antihistamines including cinnarizine, chlorphenamine, cetirizine, levocetirizine, acrivastine, fexofenadine and desloratadine (18.1%), followed by second line not ondansetron including propulsives (8.6%) and other antiemetic including peppermint and antinauseants (1.3%)

used as a first therapy (2.75%), but the preferred second choice of therapy for NVP in the UK. The figure shows that the first choice antiemetics for women giving birth between 2015 and 2019 in the UK was first-line antihistamines as defined by RCOG including cyclizine, prochlorperazine, promethazine and chlorpromazine (69.3%), other antihistamines including cinnarizine, chlorphenamine, cetirizine, levocetirizine, acrivastine, fexofenadine and desloratadine (18.1%), followed by second-line not ondansetron including propulsives (8.6%) and other antiemetic including peppermint and antinauseants (1.3%).

3.4 | Factors related to ondansetron prescriptions

Table 2 shows maternal characteristics broken down by treated and untreated nausea compared with those with no recorded nausea. The characteristics of women treated for NVP tend to differ in several ways to women without NVP. Folic acid use tends to be higher, and women with multiple pregnancies and with female infants were more often diagnosed with NVP. Women with depression, anxiety, psychosis and asthma were also more often diagnosed with NVP.

Table A4 shows the most extreme imbalances in exposures (using ATC codes level 3) to other drugs between women experiencing nausea ($n = 28\,449$) *vs*. those not experiencing nausea ($n = 611\,019$) during and before (7 to 1 mo before LMP) pregnancy. Women who experience nausea before or during pregnancy were more likely to have concomitant medications including antidepressants, treatments for bacterial infections and allergies and opioids among others.

4 | DISCUSSION

Our analysis, based on GP data across the UK, showed a steady increase in the reporting of both mild and severe NVP/HG and with a simultaneous increase in the prescription fills of ondansetron during pregnancies between 2005 and 2019. Prescription fills of ondansetron to treat NVP/HG are mainly used as a second-line treatment in the UK, with only limited use as first-line treatment (2.75%) and therefore in line with the RCOG guidelines. In total, 40% of ondansetron exposure started in the first trimester.

NVP tended to be more common in mothers with a higher body mass index, with a multiple pregnancy and with female infants. Women with underlying comorbidities such as depression, anxiety, psychosis, asthma and those exposed to high dose of folic acid were also more likely to experience NVP. Our study also demonstrated that women with NVP had a higher prior use of prescription drugs than women who did not have NVP.

The number of women with NVP, as reported by GPs in the UK, is considerably less than reported from prior questionnaire based studies.[22] This could be explained by the fact in that the majority of NVP is mild to moderate and that women can self-manage it with OTC medication and life style changes, so there is no need to see the GP about this. Nevertheless, the use of ondansetron to treat NVP in the UK has been increasing over recent years, although its proportion among commonly used antiemetics is still small compared to the USA.[12] In Norway, by contrast, <1% of NVP cases were treated with ondansetron.[11] These differences might reflect prescribing traditions and the availability of alternative products recommended in national guidelines.

Our findings confirm previous studies[23,24] that twin pregnancies and pregnancies with female foetuses were more likely to have NVP. Although the risk of developing severe NVP is small, the impact of NVP and HG on hospital admission and psychological wellbeing is substantial with 18% of women reporting post-traumatic stress and some women expressing a desire to end their pregnancy as a consequence of NVP/HG.[25] In a nationwide population-based cohort from the UK, however, no difference was observed in the proportion of women with subsequent pregnancies between women with and without HG in their first pregnancy.[26]

Although ondansetron is mainly prescribed as second-line treatment for NVP in the UK, the prescription as first-line treatment should not be overlooked. RCOG guidelines provide recommendations for ondansetron to be used as second-line treatment, while it is notable that the UK summaries of product characteristics for all 4 first-line treatments (cyclizine, prochlorperazine, promethazine, chlorpromazine) recommend avoiding use in pregnant women. For promethazine and chlorpromazine this advice is qualified by the phrase "unless the physician considers it essential". Our study has also shown that the observed daily doses (median 7.3 mg) are lower than the recommended daily doses by the clinicians (median 11.5 mg). Variation between recommended and observed doses appear to be influenced by underlying conditions such as anxiety or depression, making suboptimal management a clinical concern. Another element warranting

TABLE 2 Characteristics of women with and without antiemetic medication prescription fillings during pregnancy, IMRD-UK, 2015–2019

		Any ondansetron		Other antinauseants		Untreated nausea		No nausea	
Background characteristics (continuous variables)									
Characteristic		*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Maternal age (y)		2405	29.2 (5.5)	24 725	29.4 (5.7)	3449	28.5 (5.8)	134 407	30.5 (5.7)
BMI (kg/m^2)		1575	26.8 (6.5)	16 828	26.8 (6.7)	2279	26.1 (6.7)	85 020	26.0 (6.2)
Weight (kg)		1575	72.3 (18.5)	16 826	72.0 (17.8)	2279	70.1 (17.2)	85 020	70.3 (16.5)
Height (m)		1575	1.64 (0.07)	16 826	1.64 (0.07)	2279	1.64 (0.07)	85 020	1.64 (0.07)
Background characteristics (categorical variables)									
Characteristic		*n*	%	*n*	%	*n*	%	*n*	%
Sex of child	M	1162	48.3	12 193	49.3	1727	50.1	69 604	51.8
	F	1243	51.7	12 532	50.7	1722	49.9	64 803	48.2
Multiple births	1	2350	97.7	24 245	98.1	3378	97.9	132 270	98.4
	≥ 2	55	2.3	480	1.9	71	2.0	2137	1.6
Smoking in pregnancy	NK	620	25.8	5334	21.6	815	23.6	35 877	26.7
	No	980	40.8	9723	39.3	1347	39.1	52 621	39.2
	Ex	484	20.1	5678	23.0	781	22.6	29 156	21.7
	Yes	321	13.4	3990	16.1	506	14.7	16 753	12.5
PrescribedFolic acid	No	2196	91.3	22 907	92.7	3250	94.2	128 808	95.8
	Yes	209	8.7	1818	7.3	199	5.8	5599	4.2
Comorbidities									
Psychosis	Yes	139	7.4	1200	6.4	151	6.8	2996	3.5
Anxiety	Yes	182	9.7	1450	7.8	157	7.0	3666	4.3
Asthma	Yes	120	6.4	1314	7.1	121	5.4	3187	3.7
Depression	Yes	245	13.1	2088	11.2	235	10.5	5239	6.1
Diabetes	Yes	27	1.4	258	1.4	25	1.1	1026	1.2
Eating disorder	Yes	6	0.3	30	0.2	4	0.2	70	0.1
Epilepsy	Yes	4	0.2	19	0.1	4	0.2	68	0.1
Hypothyroid	Yes	5	0.3	79	0.4	7	0.3	407	0.5
Personality disorder	Yes	10	0.5	48	0.3	1	0.0	69	0.1

SD = standard deviation; BMI = body mass index; M = male; F = female; NK = not known; Ex = ex-smoker.

further investigation is that ondansetron is prescribed for up to 4 exposure episodes and may also be given for lengthy single exposures, indicating a long treatment duration.

Updated clinical guidelines for NVP are therefore essential in guiding clinicians on prescribing choices. Current clinical practice is based on clinical judgement with inconclusive evidence on the benefits and harms of ondansetron.[10] Prescribing ondansetron and the risks associated with it should outweigh the risks caused to the mother and foetus from potential serious sequalae of NVP.

Our findings must be interpreted bearing in mind their limitations. For our analyses, we relied on primary care medical records extracted from general practices across the UK. This means that the researchers have limited information regarding the actual use of the prescribed product—although refills of the prescriptions may allow reasonable inferences to be made. Despite having the NVP diagnosis to identify antiemetic prescriptions in our study, we cannot exclude the possibility that these medications may also have been prescribed for other coinciding indications. Although it is fair to assume that a new prescription for 1 of these drugs, in association with a diagnosis of nausea, is given for this indication. Moreover, we could not include OTC antiemetics, which may have been used prior to prescription antiemetics. Consequently, our classification of first line treatments only refers to the prescribed antiemetics. The rates of ondansetron as first-line therapy may be lower in real life if OTC treatments had been captured. Finally, our study only focused on live births and did not include *mild* NVP.

A strength of our study was that women were followed longitudinally over time, which allowed us to describe the switching patterns over time in a real-world setting. It also allowed us to study the medical history of the women starting 7 months prior to the pregnancy and identify an increased use of other drugs among women with and without NVP. More importantly, given that the data are sourced from general practices around the UK, our findings can be considered externally valid to the UK population.

5 | CONCLUSION

Ondansetron is increasingly being prescribed off-label as a treatment for NVP/HG in the UK. Although it is rarely used as a first-line prescription antiemetic treatment, it is the preferred second-line option over other on-prescription antiemetics in pregnancy. In this study, we also found that women with NVP and ondansetron prescriptions differ from their counterparts with respect to prescribed folic acid, asthma and mental health disorders. These factors may also be related to the health of the mother and child and hence should be considered as potential confounders in aetiological studies of the effects of antiemetics on pregnancy outcomes.

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IQVIA Medical Research Data (IMRD) incorporates data from THIN, a Cegedim Database.

COMPETING INTERESTS

All authors reported no conflict of interest. H.N. is a member of the EMA PRAC. The other authors are employed by EMA.

CONTRIBUTORS

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The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or 1 of its committees or working parties.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX A.

TABLE A1 Read codes used for nausea in pregnancy

Code	Description	Severity
L13..11	Hyperemesis gravidarum	1
L13..00	Excessive pregnancy vomiting	1
L130.00	Mild hyperemesis gravidarum	1
L130000	Mild hyperemesis unspecified	1
L13..12	Hyperemesis of pregnancy	1
L131.00	Hyperemesis gravidarum with metabolic disturbance	1
L130z00	Mild hyperemesis gravidarum NOS	1
L132.00	Late vomiting of pregnancy	1
L130200	Mild hyperemesis-not delivered	1
L131z00	Hyperemesis gravidarum with metabolic disturbance NOS	1
L131000	Hyperemesis gravidarum with metabolic disturbance unspecified	1
L131200	Hyperemesis gravidarum with metabolic disturbance—not del	1
L130100	Mild hyperemesis-delivered	1
L132z00	Late pregnancy vomiting NOS	1
L132000	Late pregnancy vomiting unspecified	1
L132100	Late pregnancy vomiting—delivered	1
L131100	Hyperemesis gravidarum with metabolic disturbance—delivery	1
L132200	Late pregnancy vomiting—not delivered	1
L130.11	Morning sickness	2
L13z.00	Unspecified pregnancy vomiting	2
L13zz00	Unspecified pregnancy vomiting NOS	2
L13y.00	Other pregnancy vomiting	2
L13yz00	Other pregnancy vomiting NOS	2
L13z000	Unspecified pregnancy vomiting unspecified	2
L13y000	Other pregnancy vomiting unspecified	2
L13z200	Unspecified pregnancy vomiting—not delivered	2
L13y200	Other pregnancy vomiting—not delivered	2
L13z100	Unspecified pregnancy vomiting—delivered	2
L13y100	Other pregnancy vomiting—delivered	2

1 = severe NVP/HG;2 = moderate or mild NVP; NOS = not otherwise specified.

TABLE A2 Codes for other nausea

Code	Description
198..00	Nausea
198..11	C/O—nausea
198..12	Nausea symptoms
1982.00	Nausea present
1983.00	Morning nausea
1984.00	Upset stomach
1984.11	Upset tummy
198Z.00	Nausea NOS
199..00	Vomiting
199..11	C/O—vomiting
199..12	Emesis
199..14	Vomiting symptoms
1992.00	Vomiting
1992.12	Bilious attack
1993.00	Projectile vomiting
1994.00	Vomiting blood—fresh
1994.11	Blood in vomit—symptom
1995.00	Vomiting blood—coffee ground
1996.00	Vomiting—bile stained
1997.00	Retching
199Z.00	Vomiting NOS

C/O = complaints of; NOS = not otherwise specified.

TABLE A3 Product codes for ondansetron in IMRD-UK

Code	Description
52 684 979	Ondansetron 4 mg/5 mL oral solution sugar free
66 569 979	Ondansetron 4 mg/5 mL oral solution sugar free
81 572 998	Ondansetron 8 mg orodispersible tablets
81 575 998	Ondansetron 4 mg orodispersible tablets
82 188 998	Ondansetron 4 mg/5 mL oral solution sugar free
82 637 978	Ondansetron 8 mg orodispersible films sugar free
82 638 978	Ondansetron 8 mg orodispersible films sugar free
82 639 978	Ondansetron 4 mg orodispersible films sugar free
82 640 978	Ondansetron 4 mg orodispersible films sugar free
85 762 998	Ondansetron 8 mg/4 mL solution for injection ampoules
85 763 998	Ondansetron 4 mg/2 mL solution for injection ampoules
85 765 998	Ondansetron 8 mg/4 mL solution for injection ampoules
85 766 998	Ondansetron 4 mg/2 mL solution for injection ampoules
85 865 998	Ondansetron 8 mg/4 mL solution for injection ampoules
85 866 998	Ondansetron 4 mg/2 mL solution for injection ampoules
85 867 998	Ondansetron 8 mg tablets
85 868 998	Ondansetron 4 mg tablets
86 326 979	Ondansetron 4 mg oral lyophilisates sugar free
88 905 998	Ondansetron 16 mg suppositories
88 907 998	Ondansetron 16 mg suppositories
89 001 997	Ondansetron 8 mg oral lyophilisates sugar free
89 001 998	Ondansetron 4 mg oral lyophilisates sugar free
89 197 998	Ondansetron 4 mg/5 mL oral solution sugar free
90 463 996	Ondansetron 8 mg oral lyophilisates sugar free
90 463 997	Ondansetron 4 mg orodispersible tablets
90 463 998	Ondansetron 4 mg/5 mL oral solution sugar free
93 315 990	Ondansetron 8 mg/4 mL solution for injection ampoules
93 546 996	Ondansetron 8 mg/4 mL solution for injection ampoules
93 546 997	Ondansetron 8 mg tablets
93 546 998	Ondansetron 4 mg tablets
93 548 996	Ondansetron 8 mg/4 mL solution for injection ampoules
93 548 997	Ondansetron 8 mg tablets
93 548 998	Ondansetron 4 mg tablets
95 834 979	Ondansetron 8 mg/4 mL solution for injection ampoules
95 858 979	Ondansetron 4 mg tablets

TABLE A4 Other drug exposure before and during pregnancy

	Before pregnancy		During pregnancy	
	Women with nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n	Women with no nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n
Antiemetics and antinauseants	NA	NA	699	1291
Vitamin B1, plain and in combination with vitamin B6 and B12	NA	NA	75	105
Propulsives	546	75	1615	1283
Antipsychotics	2070	282	4346	2266
Antihistamines for systemic use	5929	620	12 460	4989
Electrolytes with carbohydrates	NA	NA	775	250
Antacids	NA	NA	541	79
Drugs for treatment of peptic ulcer	6639	643	17 582	2202
Drugs for constipation	4048	374	10 234	1268
Hypnotics and sedatives	1395	158	617	74
Antidepressants	12 654	1464	9193	1091
Antimigraine preparations	1787	213	881	100
Other antibacterials	4741	459	7746	875
Drugs for functional gastrointestinal disorders	1217	135	491	53
Antiregurgitants—old code	NA	NA	2489	265
Corticosteroids for systemic use, plain	1619	168	1704	179
Direct acting antivirals	969	82	1026	106
Other β-lactam antibacterials	750	64	5957	606
Anxiolytics	2242	226	1138	114
Other analgesics and antipyretics	1993	187	4323	433
Tetracyclines	2495	255	702	70
Opioids	7206	752	8326	826
Antimycotics for systemic use	1749	136	575	57
Sulfonamides and trimethoprim	4423	418	2990	295
Calcium	NA	NA	708	68
Intestinal anti-infectives	NA	NA	719	68
Cough suppressants, excl. combinations with expectorants	1161	111	2785	262
Vitamin a and d, incl. combinations of the 2	823	68	1391	129
Antiepileptics	1609	173	1208	111
Adrenergics, inhalants	6608	635	8858	805
Topical products for joint and muscular pain	1413	147	1385	123

TABLE A4 (Continued)

	Before pregnancy		During pregnancy	
	Women with nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n	Women with no nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n
Chemotherapeutics for topical use	NA	NA	694	61
Vitamin b12 and folic acid	4951	416	23 951	2067
Other dermatological preparations	1194	90	1244	107
Decongestants and antiallergics	1033	101	1690	145
Beta blocking agents	2429	249	2055	176
Bacterial and viral vaccines, combined	NA	NA	4357	372
Decongestants and other nasal preparations for topical use	4012	365	5892	503
Anti-infectives	1481	114	1605	137
Dermatologicals	872	56	1425	121
Anti-inflammatory and antirheumatic products, nonsteroids	8238	803	2916	247
Beta-lactam antibacterials, penicillins	14 744	1217	24 130	2020
Agents for treatment of hemorrhoids and anal fissures for topical use	1567	113	5110	424
Antiacne preparations for topical use	2354	207	1630	135
Other antiasthmatics, inhalants	2481	201	3302	273
Antiinfectives and antiseptics, excl. Combinations with corticosteroids	3470	315	15 584	1280
Viral vaccines	848	68	3442	282
Iron preparations	3273	275	29 337	2354
Antifungals for topical use	3595	283	8288	658
Antibiotics for topical use	1094	84	1678	133
Corticosteroids, plain	4837	355	6456	499
Macrolides and lincosamides	3523	323	3215	247
Emollients and protectives	4173	332	6853	503
Throat preparations	1278	108	976	65
Insulins and analogues	NA	NA	1953	130
Progestogens	2290	220	1748	116
Other vitamin products, combinations	NA	NA	960	63
All other nontherapeutic products	NA	NA	4416	289
Antithrombotic agents	NA	NA	8132	526
Corticosteroids, combinations with antibiotics	NA	103	1531	98

(Continues)

TABLE A4 (Continued)

	Before pregnancy		During pregnancy	
	Women with nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n	Women with no nausea ($n = 28\,449$) Total n	Women with no nausea ($n = 611\,019$) Total n
Drugs used in addictive disorders	NA	NA	1269	76
Hormonal contraceptives for systemic use	19 717	1320	2844	167
Thyroid preparations	2796	156	3309	179
Quinolone antibacterials	464	56	NA	NA
Belladonna and derivatives, plain	1096	119	NA	NA
Antifibrinolytics	929	111	NA	NA
Anaesthetics, local	1082	103	NA	NA

NA = not available as not prescribed before or during pregnancy; No Nausea = no nausea diagnostic code in pregnancy; Nausea = corresponds to codes in Table 1. And Table 2. to Appendix.