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

Jim Slattery1 | Chantal Quinten1 | Gianmario Candore1 | Luis Pinheiro1 | Robert Flynn1,2 | Xavier Kurz1 | Hedvig Nordeng3,4

1Data Analytics Taskforce, European Medicines Agency, Amsterdam, The Netherlands
2Medicines Monitoring Unit, University of Dundee, Dundee, UK
3PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway
4Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

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

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INTRODUCTION

Nausea and vomiting affects up to 80% of pregnant women worldwide and is the most common medical condition in pregnancy. 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 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 and is associated with an increased risk of preterm birth.

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 and if symptoms are severe or persist, pharmacological therapy is recommended, but universal national guidelines for treatment of NVP are lacking.

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). Over recent years, it is increasingly used off-label in European countries as a treatment for severe NVP and to prevent progression to HG.

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. 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. 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. In 2014, it was the most common treatment for NVP in the US (25% of all pregnancies). 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.

Studies have questioned the safety of ondansetron use in the first trimester of pregnancy. Two large studies from the USA 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 Authorization 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.

Given the debate and increasing ondansetron use, the aim of this study was to characterize the utilization patterns of antiemetics in
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 treat-
ment. 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,\textsuperscript{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 (for-
merly known as THIN), release January 2020.\textsuperscript{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,
derprivation 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,\textsuperscript{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 prac-
tice 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

\begin{table}[h]
\centering
\begin{tabular}{ll}
\hline
\textbf{Table 1} & Royal College of Obstetricians and Gynaecologists
\textit{Green-top Guideline No 69 (3)}
\hline
\textbf{First-line treatment of NVP} & \\
\hline
- Cyclizine 50 mg PO, IM or IV 8 hourly & \\
- Prochlorperazine 5–10 mg 6–8 hourly PO; 12.5 mg 8 hourly & \\
\hline
- 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 & \\
\hline
\textbf{Second-line treatment of NVP} & \\
\hline
- 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 & \\
\hline
\textbf{Third-line treatment of NVP} & \\
\hline
- 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 & \\
\hline
\end{tabular}
\end{table}

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

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.\textsuperscript{7} First-line treat-
ments included cyclizine, prochlorperazine, promethazine and/or
chlorpromazine. In addition to ondansetron, second-line treatments
included metoclopramide and/or domperidone. Third-line prescrip-
tions 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 pre-
ceded by a prescription of another antiemetic.

2.5 | Exposure time frames

Exposure to antiemetics was defined as the presence of at least 1 pre-
scription 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 comediations.
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, 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 (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
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 2015–2019. 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 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.
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, 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 tended to have a higher prior use of prescription drugs than women who did not have NVP.

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. 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 lifestyle 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. In Norway, by contrast, <1% of NVP cases were treated with ondansetron. These differences might reflect prescribing traditions and the availability of alternative products recommended in national guidelines.

Our findings confirm previous studies 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. 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.

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...
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. Prescribing ondansetron and the risks associated with it should outweigh the risks caused to the mother and foetus from potential serious sequelae 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.

### Table 2

| Characteristics (continuous variables) | Any ondansetron | Other anti-nauseants | Untreated nausea | No nausea |
|---------------------------------------|-----------------|----------------------|-----------------|-----------|
| **Maternal age (y)**                  | n               | Mean (SD)            | n               | Mean (SD) |
| BMI (kg/m²)                           | 2405            | 29.2 (5.5)           | 24 725          | 29.4 (5.7) |
| Weight (kg)                           | 1575            | 26.8 (6.5)           | 16 828          | 26.8 (6.7) |
| Height (m)                            | 1575            | 1.64 (0.07)          | 16 826          | 1.64 (0.07) |

| Characteristics (categorical variables) | Any ondansetron | Other anti-nauseants | Untreated nausea | No nausea |
|-----------------------------------------|-----------------|----------------------|-----------------|-----------|
| **Sex of child**                        | n               | %                    | n               | %         |
| M                                       | 1162            | 48.3                 | 12 193          | 49.3      |
| F                                       | 1243            | 51.7                 | 12 532          | 50.7      |
| Multiple births                         | 1 2350          | 97.7                 | 24 245          | 98.1      |
| ≥ 2                                     | 55              | 2.3                  | 480             | 1.9       |
| **Smoking in pregnancy**                | n               | %                    | n               | %         |
| NK                                      | 620             | 25.8                 | 5334            | 21.6      |
| No                                      | 980             | 40.8                 | 9723            | 39.3      |
| Ex                                      | 484             | 20.1                 | 5678            | 23.0      |
| Yes                                     | 321             | 13.4                 | 3990            | 16.1      |
| **Prescribed Folic acid**               | n               | %                    | n               | %         |
| No                                      | 2196            | 91.3                 | 22 907          | 92.7      |
| Yes                                     | 209             | 8.7                  | 1818            | 7.3       |

**Comorbidities**

|                  | n               | %        | n               | %        | n               | %        | n               | %        |
|------------------|-----------------|----------|-----------------|----------|-----------------|----------|-----------------|----------|
| 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.
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

Conceptualization: J.S., G.C., L.P., R.F., X.K., H.N. Methodology: J.S., X.K., H.N. Analysis: J.S., R.F. Validation: J.S., C.Q., H.N. Supervision: J.S., X.K., H.N. Drafting the manuscript: J.S., C.Q., G.C., L.P., R.F., X.K., H.N.

DISCLAIMER

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.

All authors critically reviewed the manuscript and approved the final version for submission.

DATA AVAILABILITY STATEMENT

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

ORCID

Chantal Quinten https://orcid.org/0000-0003-2691-2326

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**APPENDIX A.**

**TABLE A1** Read codes used for nausea in pregnancy

| Code    | Description                                | Severity |
|---------|--------------------------------------------|----------|
| L13.11  | Hyperemesis gravidarum                     | 1        |
| L13..0  | 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       | 1        |
|         | disturbance                                |          |
| L130200 | Mild hyperemesis not delivered             | 1        |
| L131z00 | Hyperemesis gravidarum with metabolic       | 1        |
|         | disturbance unspecified                    |          |
| L131000 | Hyperemesis gravidarum with metabolic       | 1        |
|         | disturbance unspecified                    |          |
| L131200 | Hyperemesis gravidarum with metabolic       | 1        |
|         | disturbance—not del                        |          |
| L130100 | Mild hyperemesis—delivered                 | 1        |
| L132z00 | Late pregnancy vomiting NOS                |          |
| L132000 | Late pregnancy vomiting unspecified        | 1        |
| L131100 | Hyperemesis gravidarum with metabolic       | 1        |
|         | disturbance—delivery                       |          |
| L132200 | Late pregnancy vomiting—not del            | 1        |
| L130.11 | Morning sickness                           | 2        |
| L13z.0  | Unspecified pregnancy vomiting             | 2        |
| L13zz00 | Unspecified pregnancy vomiting NOS         | 2        |
| L13y.0  | Other pregnancy vomiting                   | 2        |
| L13y00  | Other pregnancy vomiting unspecified       | 2        |
| L13z000 | Unspecified pregnancy vomiting unspecified | 2        |
| L13y000 | Other pregnancy vomiting unspecified       | 2        |
| L13z200 | Unspecified pregnancy vomiting—not del     | 2        |
| L13y200 | Other pregnancy vomiting—not del           | 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                                |
| 1982.00 | Nausea NOS                                 |
| 199..00 | Vomiting                                  |
| 199..11 | C/O—vomiting                              |
| 199..12 | Emesis                                    |
| 199..14 | Vomiting symptoms                          |
| 1992.00 | Vomiting                                  |
| 1992.12 | Bilius 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                                  |
| 1992.00 | Vomiting NOS                               |

C/O = complaints of; NOS = not otherwise specified.
| 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                              |
| Drug Category                                    | Before pregnancy | During pregnancy |
|-------------------------------------------------|------------------|------------------|
|                                                 | Women with nausea | Women with no nausea | Women with no nausea | Women with no nausea |
|                                                 | (n = 28,449)     | (n = 611,019)     | (n = 28,449)     | (n = 611,019)     |
| 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               | 1,615            | 1,283             |
| Antipsychotics                                  | 2,070            | 282              | 4,436            | 2,266             |
| Antihistamines for systemic use                 | 5,929            | 620              | 12,460           | 4,989             |
| Electrolytes with carbohydrates                 | NA               | NA               | 775              | 250               |
| Antacids                                        | NA               | NA               | 541              | 79                |
| Drugs for treatment of peptic ulcer             | 6,639            | 643              | 17,582           | 2,202             |
| Drugs for constipation                          | 4,048            | 374              | 10,234           | 1,268             |
| Hypnotics and sedatives                         | 1,395            | 158              | 617              | 74                |
| Antidepressants                                 | 12,654           | 1,464            | 9,193            | 1,091             |
| Antimigraine preparations                      | 1,787            | 213              | 881              | 100               |
| Other antibacterials                            | 4,741            | 459              | 7,746            | 875               |
| Drugs for functional gastrointestinal disorders  | 1,217            | 135              | 491              | 53                |
| Antiregurgitants—old code                      | NA               | NA               | 2,489            | 265               |
| Corticosteroids for systemic use, plain         | 1,619            | 168              | 1,704            | 179               |
| Direct acting antivirals                        | 969              | 82               | 1,026            | 106               |
| Other β-lactam antibacterials                   | 750              | 64               | 5,957            | 606               |
| Anxiolytics                                     | 2,242            | 226              | 1,138            | 114               |
| Other analgesics and antipyretics               | 1,993            | 187              | 4,323            | 433               |
| Tetracyclines                                   | 2,495            | 255              | 702              | 70                |
| Opioids                                         | 7,206            | 752              | 8,326            | 826               |
| Antimycotics for systemic use                   | 1,749            | 136              | 575              | 57                |
| Sulfonamides and trimethoprim                   | 4,423            | 418              | 2,990            | 295               |
| Calcium                                         | NA               | NA               | 708              | 68                |
| Intestinal anti-infectives                      | NA               | NA               | 719              | 68                |
| Cough suppressants, excl. combinations with expectorants | 1,161            | 111              | 2,785            | 262               |
| Vitamin a and d, incl. combinations of the 2    | 823              | 68               | 1,391            | 129               |
| Antiepileptics                                  | 1,609            | 173              | 1,208            | 111               |
| Adrenergics, inhalants                          | 6,608            | 635              | 8,858            | 805               |
| Topical products for joint and muscular pain    | 1,413            | 147              | 1,385            | 123               |

(Continues)
|                          | Before pregnancy                     | Women with nausea (n = 28,449) | Women with no nausea (n = 611,019) | During pregnancy                     | Women with no nausea (n = 28,449) | Women with no nausea (n = 611,019) |
|--------------------------|--------------------------------------|---------------------------------|------------------------------------|--------------------------------------|----------------------------------|----------------------------------|
|                          | Total n                              | Total n                         | Total n                            | Total n                              | Total n                          | Total n                          |
| Chemotherapeutics for topical use | NA                                  | NA                              | 694                                | 61                                   |
| Vitamin B12 and folic acid | 4951                                 | 416                             | 23,951                             | 2,067                                |
| Other dermatological preparations | 1194                                 | 90                              | 1,244                              | 107                                  |
| Decongestants and antiallergics | 1033                                 | 101                             | 1,690                              | 145                                  |
| Beta blocking agents     | 2,429                                | 249                             | 2,055                              | 176                                  |
| Bacterial and viral vaccines, combined | NA                                  | NA                              | 4,357                              | 372                                  |
| Decongestants and other nasal preparations for topical use | 4,012                                | 365                             | 5,892                              | 503                                  |
| Anti-infectives          | 1,481                                | 114                             | 1,605                              | 137                                  |
| Dermatologicals          | 872                                  | 56                              | 1,425                              | 121                                  |
| Anti-inflammatory and antirheumatic products, nonsteroids | 8,238                                | 803                             | 2,916                              | 247                                  |
| Beta-lactam antibacterials, penicillins | 14,744                              | 1,217                           | 24,130                             | 2,020                                |
| Agents for treatment of hemorrhoids and anal fissures for topical use | 15,567                               | 113                             | 5,110                              | 424                                  |
| Anti-acne preparations for topical use | 2,354                                | 207                             | 1,630                              | 135                                  |
| Other antiasthmatics, inhalants | 2,481                                | 201                             | 3,302                              | 273                                  |
| Antiinfectives and antiseptics, excl. Combinations with corticosteroids | 3,470                                | 315                             | 15,584                             | 1,280                                |
| Viral vaccines           | 848                                  | 68                              | 3,442                              | 282                                  |
| Iron preparations        | 3,273                                | 275                             | 29,337                             | 2,354                                |
| Antifungals for topical use | 3,595                                | 283                             | 8,288                              | 658                                  |
| Antibiotics for topical use | 1,094                                | 84                              | 1,678                              | 133                                  |
| Corticosteroids, plain   | 4,837                                | 355                             | 6,456                              | 499                                  |
| Macrolides and lincosamides | 3,523                                | 323                             | 3,215                              | 247                                  |
| Emollients and protectives | 4,173                                | 332                             | 6,853                              | 503                                  |
| Throat preparations      | 1,278                                | 108                             | 976                                | 65                                   |
| Insulins and analogues   | NA                                   | NA                              | 1,953                              | 130                                  |
| Progestogens             | 2,290                                | 220                             | 1,748                              | 116                                  |
| Other vitamin products, combinations | NA                                   | NA                              | 960                                | 63                                   |
| All other nontherapeutic products | NA                                   | NA                              | 4,416                              | 289                                  |
| Antithrombotic agents    | NA                                   | NA                              | 8,132                              | 526                                  |
| Corticosteroids, combinations with antibiotics | NA                                   | 103                             | 1,531                              | 98                                   |
|                               | Before pregnancy |          | During pregnancy |          |
|-------------------------------|------------------|----------|------------------|----------|
|                               | Women with nausea (n = 28 449) | Women with no nausea (n = 611 019) | Women with no nausea (n = 28 449) | Women with no nausea (n = 611 019) |
| Drugs used in addictive disorders | NA               | NA       | 1269             | 76       |
| Hormonal contraceptives for systemic use | 19 717           | 1 320    | 2844             | 167      |
| Thyroid preparations          | 2 796            | 156      | 3 309            | 179      |
| Quinolone antibacterials       | 464              | 56       | NA               | NA       |
| Belladonna and derivatives, plain | 1 096           | 119      | NA               | NA       |
| Antifibrinolytics              | 929              | 111      | NA               | NA       |
| Anaesthetics, local           | 1 082            | 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.