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ORIGINAL RESEARCH

Antiemetic Prescription Fills in Pregnancy: A Drug Utilization Study Among 762,437 Pregnancies in Norway

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Objective: To determine antiemetic prescription fill patterns during pregnancy in Norway, with special focus on the use of ondansetron and recurrent use in subsequent pregnancies.

Methods: We conducted a population-based registry study based on data from the Medical Birth Registry of Norway linked to the Norwegian Prescription Database for 762,437 pregnancies >12 gestational weeks ending in live or non-live births between 2005 and 2017. Prescription fills of medications used for nausea and vomiting of pregnancy were summarized in treatment pathways to determine drug utilization patterns. Logistic regression analyses were used to estimate associations between maternal and pregnancy characteristics and antiemetic prescription fills.

Results: The prescription fill rate for antiemetic medication during pregnancy was 7.6%. However, prescription fill rates were 35.5% in the second pregnancy after filling an antiemetic prescription in the first pregnancy and 53.5% for women who filled antiemetic prescriptions in the previous 2 pregnancies. Among pregnancies with antiemetic prescription fills, 62.2% were dispensed metoclopramide, 28.2% meclizine, and 17.2% promethazine. First-line treatment started with monotherapy in 97.4% of these pregnancies, which was the only treatment received in 78.7%. Prescriptions for ondansetron were filled in 0.3% of pregnancies, with 76.9% being initially filled in the first trimester. Ondansetron as first-line prescription medication and/or use in the first trimester was associated with proxies for more severe nausea and vomiting of pregnancy, including a diagnosis of hyperemesis gravidarum, multiple gestations, a higher obstetric comorbidity index, and concomitant use of medication for gastroesophageal reflux disease and nervous system medications. Women who filled an antiemetic prescription in their first pregnancy were less likely to have subsequent pregnancies than women who did not fill an antiemetic prescription in their first pregnancy (OR 0.93, 95% CI 0.90–0.96).

Conclusion: Complex patterns of antiemetic prescription fills in pregnancy may mirror the challenge of optimal management of nausea and vomiting of pregnancy in clinical practice, especially for women with severe symptoms.

Keywords: hyperemesis gravidarum, MBRN, metoclopramide, nausea and vomiting of pregnancy, NorPD, ondansetron

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Introduction

Nausea and vomiting is the most common pregnancy-related condition, affecting up to 70% of pregnant women.[1] The symptoms typically occur during the first trimester, varying in severity from mild to life-threatening. Hyperemesis gravidarum is among the latter, affecting 1% of the pregnant population.[1] It is

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characterized by persistent nausea and vomiting, dehydration, electrolyte and nutritional imbalances, and excessive weight loss, and the most common reason for hospitalization during the first part of pregnancy.[2] Nausea and vomiting is generally not associated with adverse pregnancy outcomes,[3] although hyperemesis gravidarum has been associated with an increased risk of preterm birth, low birth weight, and small-for-gestational age.[4] Nevertheless, treatment of nausea and vomiting during pregnancy is recommended because of its detrimental impact on daily life functioning and quality of life,[5,6] and to prevent progression to hyperemesis gravidarum.

No uniform international guideline for the treatment of nausea and vomiting of pregnancy currently exists.[7] The majority of national clinical treatment guidelines recommend to first consider non-pharmacologic options, such as lifestyle and dietary changes.[3,8,9] If symptoms are severe or persist, pharmacologic therapy is recommended, but treatment algorithms vary between guidelines reflecting differences in marketed products and prescribing traditions. As a result, antiemetic drug utilization patterns differ considerably between countries. For example, in the United Kingdom antihistamines (ie, promethazine and cyclizine) and prochlorperazine are the most commonly used antiemetics, followed by metoclopramide as second-line therapy,[10] whereas in the United States ondansetron was used in nearly one in four pregnancies in 2014.[11] Most clinical guidelines recommend reserving use of ondansetron if other treatments have failed and delaying use until after 10 weeks' gestation.[3,9,12–17]

In 2019, the European Medicines Agency (EMA) recommended to avoid the use of ondansetron in the first trimester,[18] after publication of several epidemiological studies showing associations with small increased risks of oral clefts (three additional cases per 10,000 exposed to ondansetron in the first trimester) and inconclusive results on the risk of cardiac malformations.[19–22] Insight into how nausea and vomiting of pregnancy is pharmacologically managed in the real world is especially warranted in light of these recommendations, especially since the EMA recommendation is not undisputed.[23,24] Therefore, we conducted a population-based register study to determine antiemetic prescription fill patterns during pregnancy, with a special focus on ondansetron use in the first trimester, and factors associated with antiemetic prescription fills, in particular the impact of antiemetic use for a subsequent pregnancy.

Materials and Methods

We used individual-level data from the Medical Birth Registry of Norway (MBRN) and the Norwegian Prescription Database (NorPD). These registries were linked using an encrypted version of the unique personal identification number assigned to every citizen of Norway. This study was approved by the Regional Committee for Research Ethics in South Eastern Norway (approval number 2018/140/REK SørØst) and by the Data Protection Officer at the University of Oslo (approval number 58033).

Data Sources

The MBRN is a nationwide population-based registry established in 1967, containing information on >2.3 million births. It is based on mandatory notifications of all pregnancies ending after gestational week 12, including elective terminations and late miscarriages. The MBRN includes information on maternal demographics, maternal health before and during pregnancy, pregnancy complications, labor interventions, gestational age at birth, as well as information on the infant, including vital status, birth weight, congenital malformations, and other perinatal outcomes.[25]

All Norwegian pharmacies have been obliged to send electronic data to the NorPD on all prescribed medications dispensed to individuals in outpatient care since January 2004.[26] Medications in the NorPD are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[27] In addition, information on the dates of dispensing and the number of Defined Daily Doses (DDDs) dispensed is included. As we did not have information on the actual dosage prescribed, we assumed that all women used 1 DDD of the medication per day. The NorPD does not contain information on in-hospital treatment and over-the-counter medications, except when these were prescribed.

Study Population

For the present study, we included all women with a pregnancy recorded in the MBRN in 2005–2017 who could be linked to the NorPD. We excluded pregnancies with missing information on pregnancy duration, as well as pregnancies with antiemetic exposure in the 90 days prior to the last menstrual period as these medications were by definition used for other indications than nausea and vomiting of pregnancy.

Exposure

The main exposure of interest is filled prescriptions of medications indicated for the treatment of nausea and vomiting of pregnancy according to the Norwegian clinical guidelines (eAppendix).[14]

Types of Antiemetic Medications

The ATC codes for antiemetic medication included cyclizine (R06AE03), doxylamine (R06AA09), doxylamine/pyridoxine (R06AA59), meclizine (R06AE05), metoclopramide (A03FA01), ondansetron (A04AA01), prochlorperazine (N05AB04), and promethazine (R06AD02). Over-the-counter medication not prescribed by a physician and vitamins (eg, vitamin B6/pyridoxine and vitamin B1/thiamine) were not included as exposures.

Timing of Use

We defined exposure to antiemetic medication as the presence of at least one prescription fill of the medications selected within each time frame. Time frames of interest included the entire pregnancy, pregnancy trimesters (trimester 1: 1–90 days after the last menstrual period [LMP]; trimester 2: 91–180 days after LMP; trimester 3: >180 days after LMP), and lunar months (each consisting of 28 days).

Treatment Pathways

To determine treatment pathways, we distinguished monotherapy from polytherapy and add-ons from switchers. Treatment breaks, so-called "gaps", were calculated based on filling date and the number of DDDs dispensed. In line with common drug utilization research standards (ie, drug adherence research),[28] we allowed a gap of up to 14 days between the end date of the initial prescription and the filling date of the subsequent prescription before considering it a treatment break. Definitions and graphical examples of these definitions are provided in the eAppendix.

Recurrent Use

Recurrent use was defined as an antiemetic prescription fill in a previous pregnancy and in a subsequent pregnancy.

Covariates

Information on maternal age at delivery, marital status, comorbidities (asthma, chronic hypertension, chronic renal disease, pre-existing diabetes, epilepsy, and rheumatoid arthritis), parity, plurality, diagnosis of hyperemesis gravidarum (International Classification of Diseases version 10 codes O21.0, O21.1, and O21.9), obstetric comorbidity index (adapted from Bateman et al),[29] smoking during pregnancy, and year of infant birth was derived from the MBRN. Data on concomitant medication use during pregnancy, in particular the use of antacids (3rd level ATC code A02A), medication for gastroesophageal reflux disease (3rd level ATC code A02B), musculoskeletal system medication (1st level ATC code M), and nervous system medication (1st level ATC code N), was obtained from the NorPD. Recurrent pregnancy was defined as any record of a pregnancy ending after gestational week 12, including both live and non-live births (ie elective terminations, late miscarriages after gestational week 12, and stillbirths).

Statistical Analyses

The statistical analyses were performed with Stata/MP 16.0 for Windows. In all analyses, pregnancy was the unit of observation unless noted otherwise.

Descriptive Analyses

Antiemetic prescription fills during the different time frames were estimated for all pregnancies. We also evaluated the time trends of use over the study period, both for any antiemetic medication and for the individual antiemetics. The main characteristics, comorbidities, and concomitant medications of women with and without any antiemetic prescription fills and of women with the most commonly dispensed individual antiemetic medications were evaluated by descriptive statistics, including the extent and pattern of missing information.

Antiemetic Prescription Fills in Previous Pregnancies

Most previous studies did not have longitudinal data of women from the beginning of reproductive history. To study the impact of a history of antiemetic prescription fills for subsequent pregnancies, we restricted the study population to women who had their first pregnancy in Norway in 2005–2017. As experiencing severe nausea and vomiting of pregnancy may impact a woman's willingness to become pregnant again,[5,30] we compared the proportion of women who went on to having further pregnancies and the prevalence of antiemetic prescriptions fills during that pregnancy between those with and without antiemetic prescription fills, up to the fourth pregnancy. We estimated the odds ratio and 95% confidence interval for a subsequent pregnancy to compare the frequency of a second pregnancy among women with and without

antiemetic prescription fills in the first pregnancy. Multivariable logistic regression with a complete case approach was used to adjust for all potential confounding factors identified a priori based on literature and clinical knowledge, including maternal age, civil status, comorbidities, use of selected concomitant medication, smoking, plurality, obstetric comorbidity index, pregnancy outcome, and year of delivery.[5,10,31,32] These analyses were repeated after stratification by year of delivery of the first pregnancy (2005–2011 and 2012–2017).

Treatment Pathways

Among the women who filled prescriptions for antiemetic medication during pregnancy, we determined the gestational week of initiating treatment, the number of prescription fills, and the total number of DDDs dispensed. We determined the main treatment pathways based on the most frequent two-step combinations, which are changes from one treatment to another among at least 1% of pregnancies with antiemetic medication fills.[33] Treatment steps were considered the start (date of dispensing) and the end date (calculated from the number of DDDs dispensed) of prescription fills, taking into account the allowed gap of 14 days to correct for medication possession gaps due to non-adherence.

Clinical Guidelines

We determined long-term use of metoclopramide (ie, >5 days) among pregnancies ending in 2015–2017 following an EMA safety warning in December 2013, indicating that metoclopramide should only be used for a maximum of 5 days.[34] To understand how the new recommendations on ondansetron use in pregnancy from the EMA correspond with Norwegian prescription practices prior to these recommendations, we quantified the proportion of pregnancies with ondansetron prescriptions filled in the first trimester and/or as first-line antiemetic in pregnancy. Associations between maternal/pregnancy characteristics and ondansetron prescriptions filled in the first trimester and/or as first-line antiemetic in pregnancy were estimated using multivariable logistic regression analysis, with pregnancies with antiemetic fills without ondansetron as comparator. These analyses were restricted to pregnancies with complete information on all covariates of interest. The multivariable model contained all covariates in Table 1.

Sensitivity Analyses

A substantial number of women were registered with multiple pregnancies in the MBRN, resulting in correlations between observations. To assess this, we restricted the analyses on time trends and covariates to the first pregnancy per woman in a sensitivity analysis. When restricting the analyses to the first pregnancy only, the results only changed marginally. Therefore, we only presented the results of the primary analyses.

Results

A total of 762,437 pregnancies among 475,847 women were included in this study (Figure 1). A total of 321,869 women had their first pregnancy in 2005–2017 (548,382 pregnancies in total), of which 182,347 women contributed with multiple pregnancies.

Descriptive Analyses

The prevalence of any antiemetic prescription fill during pregnancy almost doubled over the study period, from 5.3% in 2005 to 10.1% in 2017 (Figure 2). Metoclopramide was the most commonly dispensed antiemetic despite the decrease in prescription fills after 2013: among pregnancies with antiemetic prescription fills, 62.2% was dispensed metoclopramide, followed by meclizine (28.2%), and promethazine (17.2%). Prescriptions for ondansetron were filled in 0.3% of pregnancies, increasing from 0.05% in 2005 to 1.0% in 2017. In 80.7% of pregnancies in which antiemetic prescriptions were filled, a prescription was filled in the first trimester, with a peak in the third lunar month (ie, gestational week 9–12; eAppendix).

The baseline maternal and pregnancy characteristics stratified by antiemetic prescription fills are shown in Table 1. Compared with women who did not fill antiemetic prescriptions in pregnancy, women who filled antiemetic prescriptions were slightly younger (29.1 vs 30.0 years), more likely to have given birth before (59.5 vs 57.7%), to have asthma (6.0 vs 4.5%), to have a multiple gestation (2.6 vs 1.6%), to have received a diagnosis of hyperemesis gravidarum (12.4 vs 1.2%), and to have used concomitant medication, particularly medication for gastroesophageal reflux disease (8.4 vs 1.9%) and nervous system medication (17.6 vs 7.5%), and less likely to have smoked in early pregnancy (8.8 vs 10.3%). These differences were generally more profound for women who filled ondansetron prescriptions, in particular for multiparity (68.5%), multiple gestation (3.5%), hyperemesis gravidarum (42.3%), use of concomitant medication for gastroesophageal reflux disease (15.9%), and smoking (2.9%). In addition, women who filled prescriptions for ondansetron,

Table 1 Characteristics of Women with and without Antiemetic Medication Prescription Fills During Pregnancy, Norway, 2005–2017

Characteristics	No Antiemetic Medication (N = 704,199 (%))		Any Antiemetic Medication (N = 58,238 (%))		Specific Antiemetic Medication							
					Metoclopramide (N = 36,246 (%))		Meclizine (N = 16,397 (%))		Promethazine (N = 10,015 (%))		Ondansetron (N = 2307 (%))	
Maternal age												
≤24 years	105,563	(15.0)	11,370	(19.5)	7089	(19.6)	3335	(20.3)	1874	(18.7)	334	(14.5)
25–29 years	221,353	(31.4)	20,078	(34.5)	12,601	(34.8)	5835	(35.6)	3370	(33.7)	774	(33.6)
30–34 years	237,877	(33.8)	17,581	(30.2)	10,930	(30.2)	4859	(29.6)	3035	(30.3)	782	(33.9)
≥35 years	139,406	(19.8)	9209	(15.8)	5626	(15.5)	2368	(14.4)	1736	(17.3)	417	(18.1)
Civil status												
Married/cohabiting	654,048	(92.9)	53,268	(91.5)	33,151	(91.5)	15,013	(91.6)	9175	(91.6)	2151	(93.3)
Other	50,140	(7.1)	4968	(8.5)	3094	(8.5)	1384	(8.4)	840	(8.4)	155	(6.7)
No information	11		2		1		0		0		1	
Parity												
Primiparity	298,228	(42.4)	23,605	(40.5)	14,638	(40.4)	6875	(41.9)	4057	(40.5)	726	(31.5)
Multiparity	405,971	(57.7)	34,633	(59.5)	21,608	(59.6)	9522	(58.1)	5958	(59.5)	1581	(68.5)
Comorbidities												
Asthma	31,572	(4.5)	3510	(6.0)	2152	(5.9)	944	(5.8)	696	(7.0)	133	(5.8)
Chronic hypertension	3809	(0.5)	317	(0.5)	199	(0.6)	78	(0.5)	50	(0.5)	10	(0.4)
Chronic renal disease	4496	(0.6)	408	(0.7)	255	(0.7)	106	(0.7)	76	(0.8)	19	(0.8)
Pre-existing diabetes	4933	(0.7)	413	(0.7)	263	(0.7)	76	(0.5)	90	(0.9)	16	(0.7)
Epilepsy	4342	(0.6)	359	(0.6)	226	(0.6)	87	(0.5)	63	(0.6)	12	(0.5)
Rheumatoid arthritis	2767	(0.4)	257	(0.4)	165	(0.5)	67	(0.4)	52	(0.5)	14	(0.6)
Concomitant medication												
Antacids	1.009	(0.1)	492	(0.8)	343	(1.0)	172	(1.1)	75	(0.8)	32	(0.9)
Medication for GERD	13,569	(1.9)	4917	(8.4)	3335	(9.2)	1508	(9.2)	866	(8.7)	367	(15.9)
Musculoskeletal system	15,782	(2.2)	2419	(4.2)	1596	(4.4)	598	(3.7)	391	(3.9)	95	(4.1)
Nervous system	52,661	(7.5)	10,257	(17.6)	6605	(18.2)	2563	(15.6)	2183	(21.8)	537	(23.3)
Smoking in early pregnancy												
Yes	61,968	(10.3)	4385	(8.8)	2654	(8.6)	1109	(7.7)	804	(9.1)	60	(2.9)
No	541,108	(89.7)	45,719	(91.3)	28,157	(91.4)	13,269	(92.3)	7992	(90.9)	2022	(97.1)
No information	101,123		8134		5435		2019		1219		225	
Hyperemesis gravidarum												
Yes	8356	(1.2)	7194	(12.4)	4791	(13.2)	2055	(12.5)	1583	(15.8)	975	(42.3)
No	695,843	(98.8)	51,044	(87.6)	31,455	(86.8)	14,342	(87.5)	8432	(84.2)	1332	(57.7)
Obstetric comorbidity index[a]												
0	467,463	(66.4)	39,203	(67.3)	24,555	(67.8)	11,357	(69.3)	6407	(64.0)	1474	(63.9)
1	156,607	(22.2)	12,203	(21.0)	7609	(21.0)	3221	(19.6)	2221	(22.2)	520	(22.5)
≥2	80,129	(11.4)	6832	(11.7)	4082	(11.3)	1819	(11.1)	1387	(13.9)	313	(13.6)
Plurality												
Singleton	692,716	(98.4)	56,737	(97.4)	35,418	(97.7)	16,007	(97.6)	9615	(96.0)	2227	(96.5)
Multiple	11,483	(1.6)	1501	(2.6)	828	(2.3)	390	(2.4)	400	(4.0)	80	(3.5)

Note: [a]Adapted from Bateman et al.[29]
Abbreviation: GERD, gastroesophageal reflux disease.

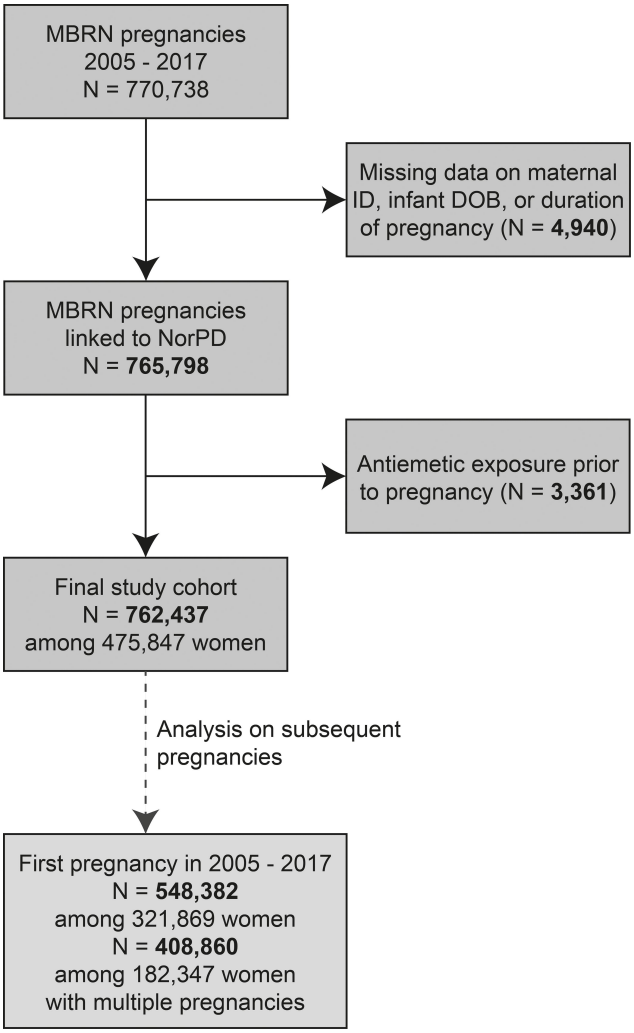

Figure 1 Flowchart of the study population.
Abbreviations: DOB, date of birth; MBRN, Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database.

prochlorperazine, or promethazine were more likely to have a higher score on the obstetric comorbidity index.

Antiemetic Prescription Fills in Previous Pregnancies

Antiemetic prescription fills in a given pregnancy are shown in Figure 3. Women who filled an antiemetic prescription in their first pregnancy were less likely to have two or more pregnancies compared to women who did not fill an antiemetic prescription in their first pregnancy (50.8 vs 57.1%; crude odds ratio [OR] 0.77, 95% confidence interval [CI] 0.75–0.80). After adjustment for confounding, the OR for having another pregnancy was closer to the null (0.93, 0.90–0.96); the observed association between antiemetic prescription fills and the likelihood of subsequent pregnancies was largely, but not completely, explained by year of delivery. Stratification by year of delivery yielded adjusted ORs for having another pregnancy of 0.86 (0.81–0.90) for 2005–2011 and 0.93 (0.89–0.98) for 2012–2017. Among women who filled an ondansetron prescription in their first pregnancy, 26.0% had two or more pregnancies (adjusted OR 0.58, 95% CI 0.47–0.71; Figure 4).

Women who had an antiemetic filled in a previous pregnancy were approximately six times more likely to have an antiemetic prescription filling in the current pregnancy compared to women with no history of antiemetic fills in a previous pregnancy (Figure 3). More specifically, antiemetic prescriptions were filled in the second pregnancy by 35.5% of women who filled an antiemetic prescription in their first pregnancy and by 6.4% of women who did not. During the third pregnancy, antiemetic prescriptions were filled by 53.5% of women who filled a prescription for antiemetics in the previous two pregnancies and decreased to 5.5% for women without a history of antiemetic medication prescription fills. The proportion of recurrent users was even higher among women who filled an ondansetron prescription in their first pregnancy (Figure 4).

Treatment Pathways

The median gestational age at initiation of antiemetic medication was 61 days (range 0–294). Women who filled prescriptions for multiple antiemetic medications during pregnancy initiated treatment earlier in pregnancy than women on monotherapy (median 54 vs 62 days, P<0.0001; eAppendix). However, ondansetron in monotherapy was initiated earlier in pregnancy than ondansetron in polytherapy (66 vs 71 days, P=0.003).

In Figure 5, the main treatment pathways are shown. In the majority of pregnancies with antiemetic medication (97.4%), first-line treatment started with monotherapy, which was the only treatment received in 78.7% of pregnancies. The median time interval between treatment initiation and the next treatment step ranged between 5 (ondansetron and prochlorperazine) and 100 days (promethazine). A treatment gap (median 25 days) after first-line treatment was observed in 8.7% of pregnancies with antiemetic medication use. In 49.6% of pregnancies, metoclopramide was the last treatment received, followed by meclizine in 22.0% of pregnancies.

In a small percentage of pregnancies, metoclopramide combined with meclizine (3.1%) or promethazine (2.3%)

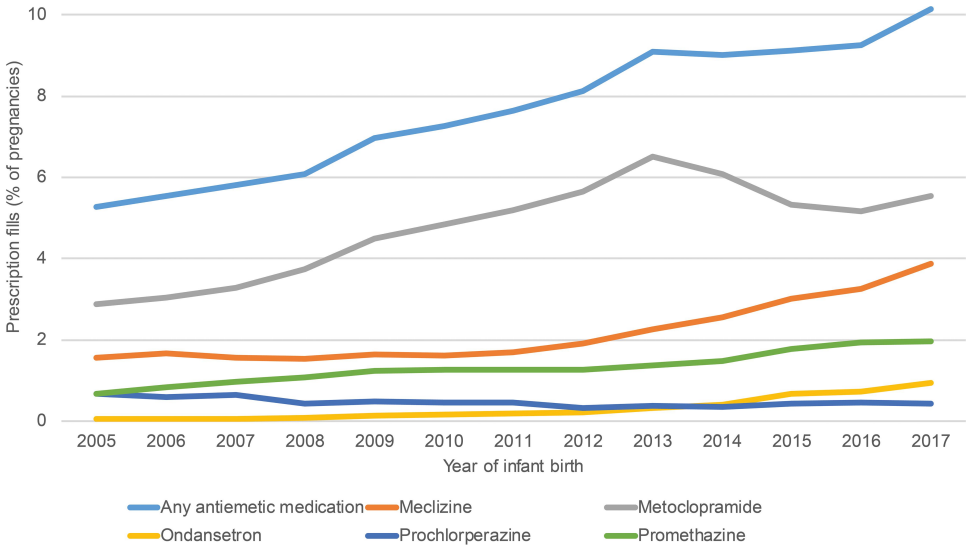

Figure 2 Secular trends of antiemetic prescription fills during pregnancy, Norway 2005–2017.

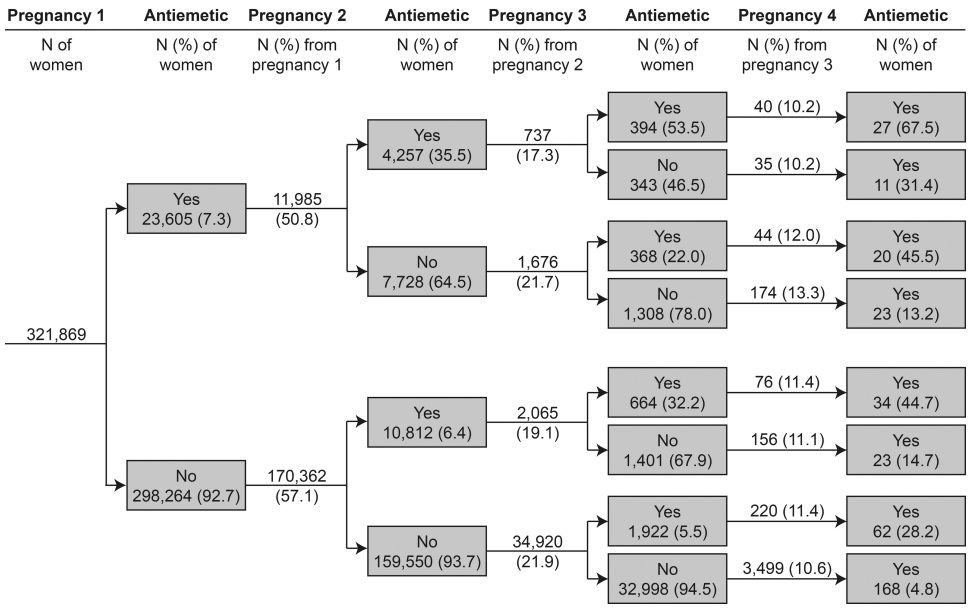

Figure 3 Prevalence of antiemetic medication fills in a given pregnancy, stratified by pregnancy order and history of antiemetic prescription fills. Data are from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2005–2017, restricted to women with their first pregnancy (irrespective of outcome) in the study period (548,382 pregnancies among 321,869 women, only first 4 pregnancies are shown).

was used. These were add-ons in most pregnancies: among pregnancies started on meclizine monotherapy, 4.0% added metoclopramide, whereas this was the case for 7.7% of pregnancies starting on promethazine monotherapy. Among pregnancies starting on metoclopramide, 1.8% and 1.4% added meclizine and promethazine, respectively.

Clinical Guidelines

Although the EMA issued a safety warning for long-term metoclopramide use in December 2013, virtually all prescriptions (99.9%) filled among pregnancies ending in 2015–2017 exceeded 5 days of use (median: 6.7 days). For pregnancies ending in 2005–2013, this applied to 90.4% of prescriptions.

In contrast to recommendations in most treatment guidelines,[3,9,12–17] ondansetron was the first filled antiemetic in 923 pregnancies (0.1% of pregnancies; 1.6% of pregnancies with antiemetic prescription fills), and ondansetron prescriptions were filled in the first trimester in 1773 pregnancies (0.2% of pregnancies; 3.0% of

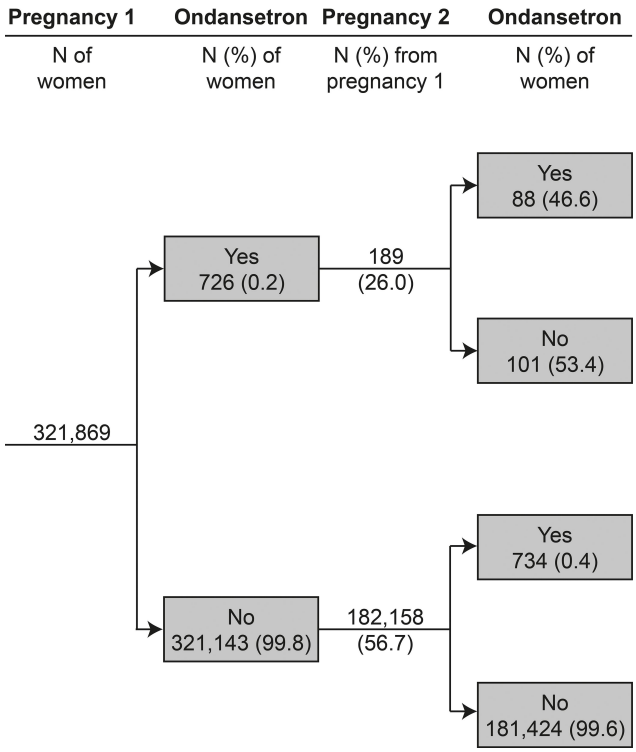

Figure 4 Prevalence of ondansetron fills in a given pregnancy, stratified by pregnancy order and history of ondansetron prescription fills. Data are from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2005–2017, restricted to women with their first pregnancy in the study period (548,382 pregnancies among 321,869 women, only first 2 pregnancies are shown due to small counts (<10) in subsequent pregnancies).

pregnancies with antiemetic prescription fills); in 0.3% of pregnancies either one of these. After adjustment for the other characteristics, women who used ondansetron as first-line treatment were slightly older, more often diagnosed with hyperemesis gravidarum (OR 4.0, 95% CI 3.4–4.6) or multiparous (1.7, 1.4–2.0), more likely to use medication for gastroesophageal reflux disease (1.6, 1.3–2.0), less likely to smoke in early pregnancy (0.3, 0.2–0.5), and had a slightly higher obstetric comorbidity index compared with women who used other antiemetics (Table 2). Pregnancies with ondansetron use in the first trimester were more likely to be among women with hyperemesis gravidarum (4.9, 4.5–5.5), multiparous women (1.7, 1.5–1.9), women who used medication for gastroesophageal reflux disease (1.7, 1.5–2.0) or nervous system medication (1.3, 1.2–1.5) during pregnancy, and non-smokers (0.3, 0.2–0.4). In addition, multiple pregnancies seemed to be more common among women who used ondansetron in the first trimester compared to women who used other antiemetics during pregnancy (1.4, 1.0–1.9).

Discussion

In this population-based registry study, we observed a strong increase in the prevalence of prescription fills for antiemetic medication during pregnancy in Norway, with over 10% of pregnant women using antiemetics in 2017, most commonly metoclopramide and antihistamines. In the majority of pregnancies, treatment with antiemetics was consistent with clinical guidelines, although long-term metoclopramide use was very common. In addition, a small proportion of pregnant women used ondansetron as first-line treatment and/or in the first trimester. The latter seemed to be associated with some proxies for more severe nausea and vomiting, including multiple pregnancies, a diagnosis of hyperemesis gravidarum, a higher obstetric comorbidity index, and concomitant use of medication for gastroesophageal reflux disease and nervous system medications. Having an antiemetic prescription fill, in particular for ondansetron, in one pregnancy is a predictor of not having a subsequent pregnancy. Although it was not a strong predictor, it warrants attention. When there were subsequent pregnancies, however, having an antiemetic prescription fill was a strong predictor for recurrence of antiemetic prescription fills.

Comparison with Other Studies

The prevalence of use observed in this study is in line with estimates from other European countries, ranging from 5.5% to 12.9%.[10,35,36] However, antiemetic medication use in pregnancy is much more common in the USA and Canada, with prevalence estimates exceeding 25%.[11,37,38] We observed an almost 20-fold increase in ondansetron prescription fills over the study period, but still this medication is not among the most commonly antiemetic prescriptions during pregnancy in Norway (<1%), in contrast to the USA where the prevalence was 22% in 2014.[11] The differences in overall prevalence and the types of antiemetics used between countries may be associated with prescribing traditions, medicinal products on the market, marketing pressures, but also attitudes towards nausea and vomiting of pregnancy among health care professionals. For example, previous studies showed that many Norwegian women reported suboptimal management of hyperemesis gravidarum and lack of support from health-care professionals.[5,30]

Comparable with previous studies,[10,37,39] antiemetic medication use was associated with younger maternal age and multiple pregnancies. The lower prevalence of

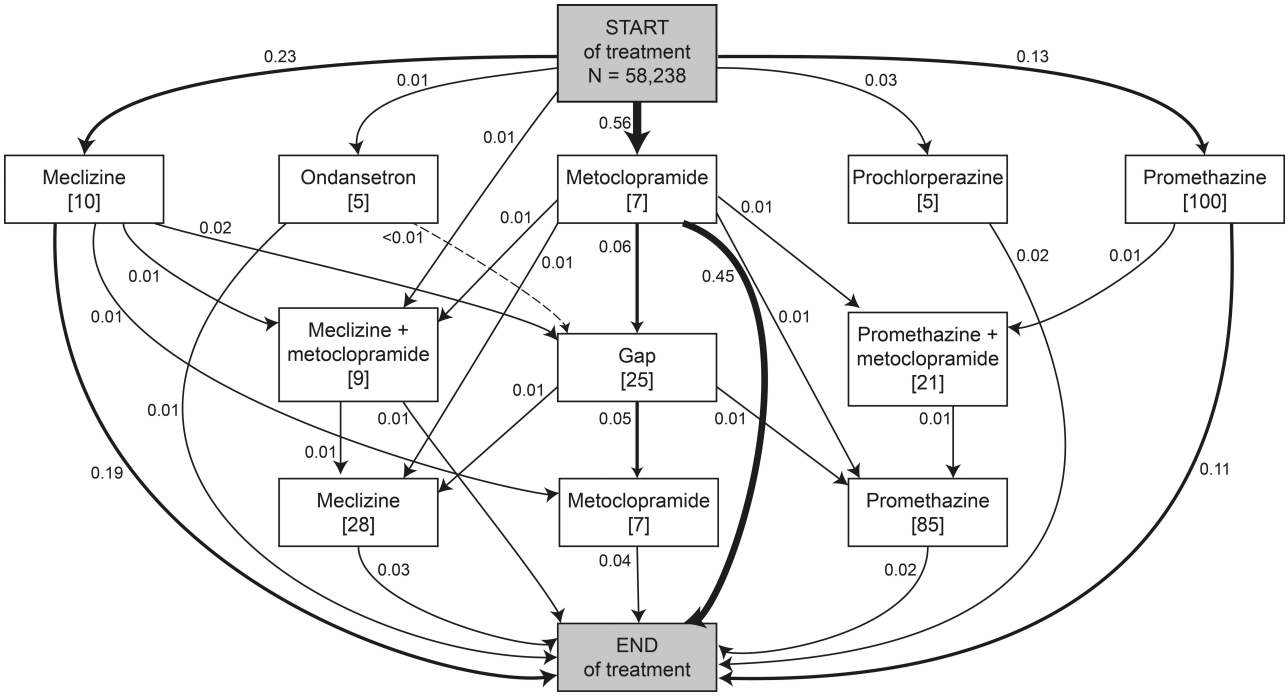

Figure 5 Main treatment pathways of antiemetic prescription fills. The numbers next to the arrows represent the proportion of pregnancies taking the represented step in the treatment path. The numbers in square brackets below the treatments represent the median number of days on this treatment. A treatment gap is defined as an interval longer than 14 days between the end date of the first treatment step and the start data of the subsequent treatment step. Proportions do not add up to 1.00 as only main pathways containing at least 1% of pregnancies (n=582) with antiemetic prescriptions fills are shown.

antiemetic medication use among non-smokers is consistent with studies from Australia[39] and the UK,[10] whereas North American studies reported that ondansetron users were up to twice as likely to smoke during pregnancy.[19,37]

To the best of our knowledge, we are among the first to follow-up women from the beginning of their reproductive history to quantify recurrent antiemetic use in subsequent pregnancies. Experiencing severe nausea and vomiting of pregnancy may impact a woman's willingness to become pregnant again.[5,30] In a previous study among women with nausea and vomiting of pregnancy in Norway, over one-fourth of women with severe nausea and vomiting of pregnancy considered terminating the pregnancy for this reason, and three in four considered not to get pregnant again.[5] Indeed, we observed women with antiemetic prescriptions in the first pregnancy, and in particular, those women who filled a prescription for ondansetron, to have fewer pregnancies compared to women without antiemetic prescriptions. This association attenuated after correction for year of delivery, which should be taken into account as women in the most recent study years may not have attempted at a subsequent pregnancy yet. In a nationwide population-based cohort study from the UK, however, no difference was observed in the proportion of women with subsequent pregnancies between women with and without hyperemesis gravidarum in their first pregnancy.[40] Hyperemesis gravidarum recurrence rates vary between 15.2% based a Norwegian population-based registry study to 80.7% according to self-reported diagnoses in the USA.[41,42] A genetic component in the etiology of severe nausea and vomiting of pregnancy and hyperemesis gravidarum has been hypothesized,[43–46] as well as a history of motion sickness, migraine, or depression.[47,48] Non-biological mechanisms could also contribute to the high recurrent use of antiemetic medication, such as the women's beliefs about medications and positive experiences associated with pharmacological treatment in a previous pregnancy.[49]

Clinical Implications

With over 70% of Norwegian women experiencing nausea with or without vomiting during pregnancy,[50] and only 10% filling antiemetic prescriptions, current management of this condition may not be optimal.[5,6] Severity of nausea and vomiting of pregnancy, as measured with the 3-item Pregnancy Unique Quantification of Emesis (PUQE) Scale,[51] is associated with quality of life,[5,52] and may be used in clinical practice to guide treatment

Table 2 Characteristics of Women Who Filled Prescriptions for Ondansetron Deviating from Treatment Guidelines, Norway, 2005–2017[a]

Characteristic	Antiemetic Medication without Ondansetron (N = 48,022)	Ondansetron as First-Line Treatment (N = 825)			Ondansetron Use in Trimester 1 (N = 1,599)		
	N (%)	N (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)	N (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Maternal age							
≤24 years	9,625 (20.0)	105 (12.7)	0.8 (0.6-0.9)	0.9 (0.7-1.2)	212 (13.9)	0.7 (0.6-0.8)	0.9 (0.8-1.1)
25-29 years	16,606 (34.6)	241 (29.2)	Reference	Reference	529 (33.1)	Reference	Reference
30-34 years	14,350 (29.9)	296 (35.9)	1.4 (1.2-1.7)	1.3 (1.1-1.5)	568 (35.5)	1.2 (1.1-1.4)	1.1 (1.0-1.3)
≥35 years	7,441 (15.5)	183 (22.2)	1.7 (1.4-2.1)	1.3 (1.0-1.8)	280 (17.5)	1.2 (1.0-1.4)	1.0 (0.8-1.2)
Civil status							
Married/cohabiting	43,972 (91.6)	776 (94.1)	Reference	Reference	1,502 (93.9)	Reference	Reference
Other	4,050 (8.4)	49 (5.9)	0.7 (0.5-0.9)	0.9 (0.6-1.2)	97 (6.1)	0.7 (0.6-0.9)	0.9 (0.7-1.1)
Parity							
Primiparity	19,739 (41.1)	222 (26.9)	Reference	Reference	447 (28.0)	Reference	Reference
Multiparity	28,283 (58.9)	603 (73.1)	1.9 (1.6-2.2)	1.7 (1.4-2.0)	1,152 (72.1)	1.8 (1.6-2.1)	1.7 (1.5-1.9)
Comorbidities							
Asthma	3,026 (6.3)	50 (6.1)	1.0 (0.7-1.3)	0.9 (0.7-1.3)	84 (5.3)	0.8 (0.7-1.0)	0.8 (0.6-1.1)
Chronic hypertension	257 (0.5)	5 (0.6)	1.1 (0.5-2.8)	0.9 (0.4-2.2)	7 (0.4)	0.8 (0.4-1.7)	0.7 (0.3-1.5)
Chronic renal disease	343 (0.7)	8 (1.0)	1.4 (0.7-2.8)	1.2 (0.6-2.4)	13 (0.8)	1.1 (0.7-2.0)	1.0 (0.6-1.8)
Pre-existing diabetes	336 (0.7)	6 (0.7)	1.0 (0.5-2.3)	1.0 (0.4-2.3)	7 (0.4)	0.6 (0.3-1.3)	0.7 (0.3-1.5)
Epilepsy	297 (0.6)	3 (0.4)	0.6 (0.2-1.8)	0.6 (0.2-1.9)	6 (0.4)	0.6 (0.3-1.4)	0.6 (0.3-1.4)
Rheumatoid arthritis	222 (0.5)	5 (0.6)	1.3 (0.5-3.2)	1.2 (0.5-2.8)	6 (0.4)	0.8 (0.4-1.8)	0.7 (0.3-1.7)
Concomitant medication							
Antacids	389 (0.8)	5 (0.6)	0.7 (0.3-1.8)	0.6 (0.2-1.4)	15 (0.9)	1.2 (0.7-1.9)	0.8 (0.5-1.4)
Medication for GERD	3,889 (8.1)	114 (13.8)	1.8 (1.5-2.2)	1.6 (1.3-2.0)	236 (14.8)	2.0 (1.7-2.3)	1.7 (1.5-2.0)
Musculoskeletal system	1,956 (4.1)	28 (3.4)	0.8 (0.6-1.2)	0.8 (0.5-1.2)	65 (4.1)	1.0 (0.8-1.3)	0.9 (0.7-1.2)
Nervous system	8,386 (17.5)	171 (20.7)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	358 (22.4)	1.4 (1.2-1.5)	1.3 (1.2-1.5)
Smoking in early pregnancy							
Yes	4,325 (9.0)	23 (2.8)	0.3 (0.2-0.4)	0.3 (0.2-0.5)	41 (2.6)	0.3 (0.2-0.4)	0.3 (0.2-0.4)
No	43,697 (91.0)	802 (97.2)	Reference	Reference	1,558 (97.4)	Reference	Reference
Hyperemesis gravidarum							
Yes	5,538 (11.5)	288 (34.9)	4.1 (3.6-4.8)	4.0 (3.4-4.6)	645 (40.3)	5.2 (4.7-5.8)	4.9 (4.5-5.5)
No	42,484 (88.5)	537 (65.1)	Reference	Reference	954 (59.7)	Reference	Reference
Obstetric comorbidity index							
0	32,423 (67.5)	494 (59.9)	Reference	Reference	1,033 (64.6)	Reference	Reference
1	9,949 (20.7)	197 (23.9)	1.3 (1.1-1.5)	1.0 (0.8-1.3)	341 (21.3)	1.1 (0.9-1.2)	1.0 (0.8-1.2)
≥2	5,650 (11.8)	134 (16.2)	1.6 (1.3-1.9)	1.2 (0.9-1.7)	225 (14.1)	1.2 (1.1-1.4)	1.1 (0.9-1.4)
Plurality							
Singleton	46,790 (97.4)	795 (96.4)	Reference	Reference	1,536 (96.1)	Reference	Reference
Multiple	1,232 (2.6)	30 (3.6)	1.4 (1.0-2.1)	1.1 (0.7-1.8)	63 (3.9)	1.6 (1.2-2.0)	1.4 (1.0-1.9)

Notes: [a]Only pregnancies with complete covariate information. A total of 14.0% of the population had missing values on covariates, of which 99.98% on smoking status in early pregnancy. [b]Adjusted for the other characteristics.

Abbreviation: GERD, gastroesophageal reflux disease.

decisions and track effects of antiemetics. It has been shown previously that many women with moderate (70%) or severe symptoms (33%) according to the PUQE Scale do not use any pharmacological treatment,[48] making suboptimal management a serious clinical concern.

In most European countries, lack of licensed antiemetics in pregnancy makes treatment of nausea and vomiting in pregnancy challenging in clinical practice. In 2018, however, delayed-release tablets containing a combination of 10 mg doxylamine and 10 mg pyridoxine was licensed for use against nausea and vomiting of pregnancy in the UK, which may improve the situation for pregnant women in this country.[53] Updated clinical guidelines for nausea and vomiting of pregnancy are therefore essential in guiding clinicians on prescribing choices.[7]

Moreover, warnings from regulators on metoclopramide and ondansetron may be challenging to translate into clinical practice. More specifically, because ondansetron use for nausea and vomiting of pregnancy or hyperemesis gravidarum has not been authorized by medicine authorities, its off-label use remains a matter of clinical judgement of the benefits and risks. According to most clinical guidelines, use of ondansetron can be justified when other treatment options fail, symptoms are severe, or recurrence risk is high.[3,9,12–17] In these situations, clinicians have an important role in explaining why their decision for prescribing deviates from the information in the product information leaflet to avoid non-adherence and fear of teratogenicity. In our study, we observed that ondansetron in monotherapy was initiated earlier in pregnancy than ondansetron in polytherapy. This indicates that women on polytherapy may have tried other medications first before initiating ondansetron treatment. Women who used ondansetron as first-line treatment, however, may have experienced earlier relief of symptoms, not needing to switch to or add-on other medications.

Research Implications

Future research may focus on optimizing treatment of nausea and vomiting of pregnancy by studying the comparative effectiveness and safety of antiemetics. Not only seem many pregnant women to refrain from pharmacologic treatment, this study showed that over 20% of pregnant women who used antiemetics needed multiple treatment steps to manage the condition. The development of more personalized treatment regimens and close surveillance of symptoms by for example digital support tools and mobile applications (eg MySafeStart, https://play.google.com/store/apps/details?id=no.uio.mobileapps.safestartandhl=en_US), may increase the efficacy of antiemetic medications and improve management of nausea and vomiting of pregnancy. Moreover, more insight into the effects of nausea and vomiting of pregnancy, hyperemesis gravidarum, and antiemetic medication use on short- and long-term maternal and child health outcomes is warranted to better inform treatment guidelines.

This study also provides a novel approach to drug utilization by visualizing antiemetic switching patterns. By describing how treatment pathways occur in the real world, this approach may promote a better understanding of the complexity of medication use in pregnancy.

Strengths and Limitations

The main strength of this study is the use of registry data from the MBRN linked to the NorPD, enabling us to generate a dataset with national coverage over a 13-years period. These registry data provided us with the unique opportunity to assess antiemetic prescription fills in a previous pregnancy, which is often impossible to assess in studies using data from registries or administrative claims databases.[54] In addition, and also in contrast to data from many other registries and claims databases,[54] over-the-counter medication prescribed by a physician is included in the NorPD, resulting in less underestimation of antiemetic medication use than those registries only including prescribed or reimbursed medications.

However, the majority of over-the-counter antiemetics use was most likely not in the NorPD: in a cross-sectional questionnaire-based study among Norwegian women with recent nausea and vomiting of pregnancy, use of meclizine, an over-the-counter medication licensed for motion sickness and not nausea and vomiting of pregnancy (10 tablet package), was reported by 23.6% of women.[49] Therefore, we may have identified only women with severe nausea and vomiting of pregnancy. The assumption of antiemetic medication use of 1 DDD per day, which is often used in drug utilization studies in which the actual dose is unavailable,[55] may have led to an underestimation or overestimation of treatment duration. Specifically, this assumption may have led to an overestimation of the duration of promethazine use (median: 100 days), as the Norwegian treatment algorithm states that pregnant women may use up to 3 DDDs to treat symptoms of

nausea and vomiting.[14] If so, the median duration would be approximately 1 month, which would still be longer than the other antiemetics. Promethazine is a second-line antiemetic and may be used for more severe nausea and vomiting of pregnancy. Alternatively, promethazine may have been prescribed for other indications. Furthermore, we did not have information on the indication for use, the severity of nausea and vomiting of pregnancy, whether or not the medication dispensed was actually taken, and the use of in-hospital medication. The latter may have resulted in an underestimation of ondansetron fills, because this antiemetic may have been administered intravenously in hospital settings. In 2.0% of pregnancies in our study, hyperemesis gravidarum was diagnosed, indicating that even if in the unlikely case that in all of these pregnancies ondansetron was administered in hospitals, the prevalence of ondansetron use stays far below estimates from the USA.

Conclusion

Antiemetic prescription fills occurred in 8% of pregnancies in Norway between 2005 and 2017. Antihistamines and metoclopramide were most frequently dispensed. Importantly, in only a very small proportion of pregnancies ondansetron was used as first-line treatment or in the first trimester. Women who filled antiemetic prescriptions, particularly for ondansetron, in their first pregnancy were less likely to have a future pregnancy. When there were future pregnancies, they were more likely to have an antiemetic prescription fill compared to women without antiemetics in their first pregnancy.

Disclosure

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