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ORIGINAL ARTICLE

New evidence for concern over the risk of birth defects from medications for nausea and vomitting of pregnancy

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Abstract

Objectives: The aim of the study was to quantify the risk of major congenital malformations (MCM) associated with first-trimester exposure to antiemetics.

Study Design and Setting: Using the Quebec Pregnancy Cohort (1998–2015), first-trimester doxylamine–pyridoxine, metoclopramide, and ondansetron exposures were assessed for their association with MCM. Generalized estimating equations were used to estimate odds ratios (OR), adjusting for potential confounders (aOR).

Results: Within 17 years of follow-up, the prevalence of antiemetic use during pregnancy increased by 76%. Within our cohort, 45,623 pregnancies were exposed to doxylamine–pyridoxine, 958 to metoclopramide, and 31 to ondansetron. Doxylamine–pyridoxine and metoclopramide use were associated with an increased risk of overall MCM (aOR 1.07, 95% confidence interval [CI]: 1.03–1.11; 3,945 exposed cases) and (aOR 1.27, 95% CI: 1.03–1.57; 105 exposed cases), respectively. Doxylamine–pyridoxine exposure was associated with increased risks of spina bifida (aOR 1.87, 95% CI: 1.11–3.14; 23 exposed cases), nervous system (aOR 1.25, 95% CI: 1.06–1.47; 225 exposed cases), and musculoskeletal system defects (aOR 1.08, 95% CI: 1.02–1.14; 1,735 exposed cases). Metoclopramide exposure was associated with an increased risk of genital organ defects (aOR 2.26, 95% CI: 1.14–4.48; 10 exposed cases). No statistically significant association was found between ondansetron exposure and the risk of overall MCM.

Conclusion: First-trimester doxylamine–pyridoxine and metoclopramide exposure was associated with a significantly increased risk of overall and specific MCM.

Keywords: Antiemetic; Doxylamine–pyridoxine; First-trimester of pregnancy exposure; Major congenital malformations; Metoclopramide; Ondansetron

1. Introduction

Nausea and vomiting of pregnancy (NVP) affects up to 80% of pregnancies [1], and it typically occurs during the first trimester, the most sensitive time for environmental exposures given organogenesis. Currently, the Society of Obstetricians and Gynecologists of Canada (SOGC) recommends pyridoxine or doxylamine–pyridoxine combination as first-line pharmacologic treatment for NPV [2] and doxylamine–pyridoxine treatment may be started preemptively at the onset of pregnancy in women at high risk for NVP [2]. Other antiemetics such as metoclopramide and ondansetron may be prescribed for the management of severe NVP [3]. A recent multinational study showed that Canada had the highest prevalence (42%) of antiemetic use for the treatment of NVP [4]. Specifically, Quebec had the highest

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Declarations of interest: none.

Ethics approval and consent to participate: The study was approved by the Sainte-Justine's Hospital Ethics Committee. The Quebec "Commission d'accès à l'information" authorized database linkages.

Availability of data and material: Diagnoses, medication, and procedure codes used in the present study are available from the corresponding author on request.

Competing interests: The authors declare that they have no competing interests.

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What is new?

Key findings

- There was a 76% increase in the prevalence of antiemetics use during pregnancy between 1998 and 2015 in the Quebec Pregnancy Cohort.
- First-trimester doxylamine–pyridoxine and metoclopramide exposure were statistically associated with an increased risk of overall major congenital malformations. Although no association was found for ondansetron, caution is warranted, given that there were only 31 exposed pregnancies in our cohort.

What this adds to what was known?

- Antiemetics are commonly used to treat nausea and vomiting of pregnancy, but conflicting information exists regarding its safety to the fetus.
- Doxylamine–pyridoxine was just reintroduced in the United States, and our study showed that it is increasing the risk of major congenital malformations.

What is the implication and what should change now?

- Our data may be used to guide clinicians in making an informed decision in the treatment of nausea and vomiting during pregnancy.

dispensation rate of doxylamine–pyridoxine among seven Canadian provinces [5].

Despite the common use of antiemetics and specifically doxylamine–pyridoxine in Canada, Persaud et al. reexamined the data used for the development of the SOGC guidelines, and found a lack of evidence on the effectiveness for this antiemetic in the treatment of NVP [6,7]. Furthermore, Chin et al. [8] reanalyzed a commonly cited meta-analysis [9] on the safety of doxylamine–pyridoxine and found a discrepancy in the number of participants and the reported odds ratio (OR), suggesting that the results may not be reliable. In the United States, the number of ondansetron exposed pregnancies markedly increased between 2006 and 2014, whereas metoclopramide exposed pregnancies decreased during the same period [10]. Of note, doxylamine–pyridoxine was only reapproved in the United States in 2013 after being taken off the market in 1983 [11]. In contrast, British guidelines for the management of NVP do not mention doxylamine–pyridoxine [12].

In the current literature, no association between metoclopramide exposure during the first trimester of pregnancy and the risk of MCM was found [13]. Anderka et al. [14] found an increased risk of cleft palate, and Danielsson et al. [15] found an increased risk of cardiovascular defect associated with ondansetron. Therefore, we aimed to quantify the risk of overall MCMs and organ system-specific MCMs associated with first-trimester exposure to doxylamine–pyridoxine, metoclopramide, and ondansetron.

2. Methods

2.1. Setting

Using the Quebec Pregnancy Cohort (QPC), we carried out this study in response to a query from Health Canada and the Drug Safety and Effectiveness Network on the effect of gestational use of antiemetic medications (doxylamine–pyridoxine, metoclopramide, and ondansetron) on the unborn child. The QPC is described in Bérard and Sheehy [16]. Briefly, the QPC is a population-based cohort with prospective data collection on all pregnancies covered by the Quebec Prescription Drug Insurance Plan administered by the Régie de l'assurance maladie du Québec (RAMQ) between January 1998 and December 2015. Information for each pregnancy is obtained from province-wide databases and linked using unique personal identifiers. All pregnancies included in the QPC were identified from the RAMQ and the Quebec hospitalization archives (MedEcho) databases. The first day of the last menstrual period (defined as the first day of gestation [1DG]) was determined using data on gestational age, which was validated against ultrasound measures in patients' charts [17]. Prospective follow-up data were available from 1 year before the 1DG, during pregnancy, and until December 2015 for all pregnancies. For pregnancies ending in live births, infants were identified using the mother–child link provided by the RAMQ database and confirmed using the Quebec Statistics database (ISQ). Follow-up data were available from birth until December 2015 for the children.

The data sources for this study include the RAMQ medical service database (diagnoses based on the International Classification of Disease [ICD] codes [ICD-9 and ICD-10], medical procedures, women's socioeconomic status, physician characteristics including medical specialty, pharmaceutical service database [drug name, start date, dosage, duration, and prescribers]), MedEcho hospitalization archive database (diagnoses [ICD-9 and ICD-10 codes], procedures, and consultations), and the ISQ (sociodemographic and vital status data, birth weight, and gestational age).

The study was approved by the Sainte-Justine's Hospital Ethics Committee. The Quebec "Commission d'accès à l'information" authorized database linkages.

2.2. Study population

A cohort of pregnancies was formed within the QPC. Eligible pregnancies were the ones that met the following inclusion criteria: (1) continuous prescription drug insurance coverage of at least 12 months before the 1DG and during pregnancy and (2) pregnancies with a liveborn singleton, given that multiplicity is associated with MCMs [18]. We excluded pregnancies exposed to known fetotoxic medications during the first trimester of pregnancy based on Briggs et al. [19] and Kulaga et al. [20] (Appendix Table S1), as well as those with newborn diagnoses of chromosomal abnormalities. We further excluded pregnancies resulting in minor malformations alone in newborns. This was done because minor malformations are likely diagnosed selectively (leading to potential outcome misclassification), and chromosomal abnormalities are likely unrelated to the medications of interest [21]. All pregnancies meeting eligibility criteria were analyzed.

2.3. Antiemetic exposures

We defined exposure to antiemetics as having filled at least one prescription for doxylamine–pyridoxine, metoclopramide, or ondansetron within the first trimester of pregnancy. The relevant exposure time window for MCMs was the first trimester (first day of the last menstrual period—98 days of gestation) confirmed by ultrasound. The reference category for all analyses was no exposure to any antiemetics during the same time window. Data on prescription fillings during pregnancy have been validated (overall exposure and exposure to antiemetics) and compared with maternal reports [22]. Specifically, the positive predictive value (PPV) for medication prescription drug data in the cohort was found to be 78% (95% CI: 62–95%), and the negative PV (NPV) was 98% (95% CI: 91–100%) [22].

2.4. Major congenital malformation outcomes

MCMs diagnosed in the first 6 months of life were identified in the RAMQ and MedEcho databases and defined according to ICD-9 and ICD-10 codes (Appendix Table S2). The use of ICD-9 and ICD-10 codes for the identification of MCMs in the QPC has been validated against medical patient charts (PPV of at least 80% and NPV of 93%) [23,24]. All organ systems were considered as well as overall MCMs. The reference group were pregnancies ending with a newborn without major or minor congenital malformation diagnosed within 6 months of life.

2.5. Covariates

We selected variables a priori, known as risk factors for MCMs or markers of disease severity. The following potential confounding variables were assessed: (1) sociodemographic variables on the 1DG including maternal age, receipt of social assistance (yes/no), and area of residence (urban/rural); (2) maternal chronic comorbidities during the year before 1DG including obesity (yes/no), diabetes (type I or type II; yes/no), hypertension (yes/no), asthma (yes/no), depression and/or anxiety and/or bipolar disorder (yes/no), epilepsy (yes/no), and tobacco and alcohol dependence (yes/no). The previous conditions were either identified from physician-based diagnoses or filled prescriptions for related medications (Appendix Table S3); (3) health care utilization during the year before 1DG including hospitalizations or emergency department visits (yes/no), number of general practitioner or specialist visits, and number of other medications used (excluding antiemetics and medications used for the identification of the previous conditions described above); (4) pregnancy-related variables including previous pregnancies, abortions, or miscarriages in the year before 1DG (yes/no) and whether the pregnancy was followed by a gynecologist (yes/no); (5) to adjust for the severity of NVP, we assessed the outpatient and inpatient diagnosis of NVP during pregnancy (yes/no); and (6) periconceptional high-dose folic acid supplementation (>5 mg/d) in the 6 months before the 1DG and during the first trimester was also included in the multivariate models.

2.6. Statistical analyses

The unit of analysis was a pregnancy. Descriptive analyses were performed to summarize the study population characteristics, using *t*-test and χ^2 tests for continuous and categorical variables, respectively. As described previously, we conducted separate analyses for overall MCMs and for each organ system malformation.

Given that a woman could be pregnant several times during the study period and meet the inclusion criteria, we used generalized estimating equations (GEE) models with logit-link function for the binary response and exchangeable correlation structure. This model takes into account within-woman correlations as well as between-subject variability. We calculated ORs and 95% CIs after controlling for potential confounders. Given that no control sampling was done (all eligible pregnancies were analyzed), GEE analyses and survival analyses give similar findings [25]. Statistical analyses were performed using SAS (SAS Institute Inc., Version 9.2, Cary, NC). Differences were considered statistically significant when the 95% CIs did not overlap 1.0 and when $P < 0.05$ (two tailed).

3. Results

The study population included 224,876 singleton live births (Fig. 1). Among the 45,623 pregnancies exposed to doxylamine–pyridoxine during the first trimester, the mean gestational age on the first prescription filled was 8.2 weeks (approximately 6.2 weeks after conception) compared with 9.4 (approximately 7.4 weeks after conception) weeks for the first metoclopramide prescription filled ($n = 958$), and 10.2 weeks (approximately 8.4 weeks after conception) for the first ondansetron prescription filled ($n = 31$). The mean number of exposed days during the first trimester was higher among the doxylamine–pyridoxine exposed

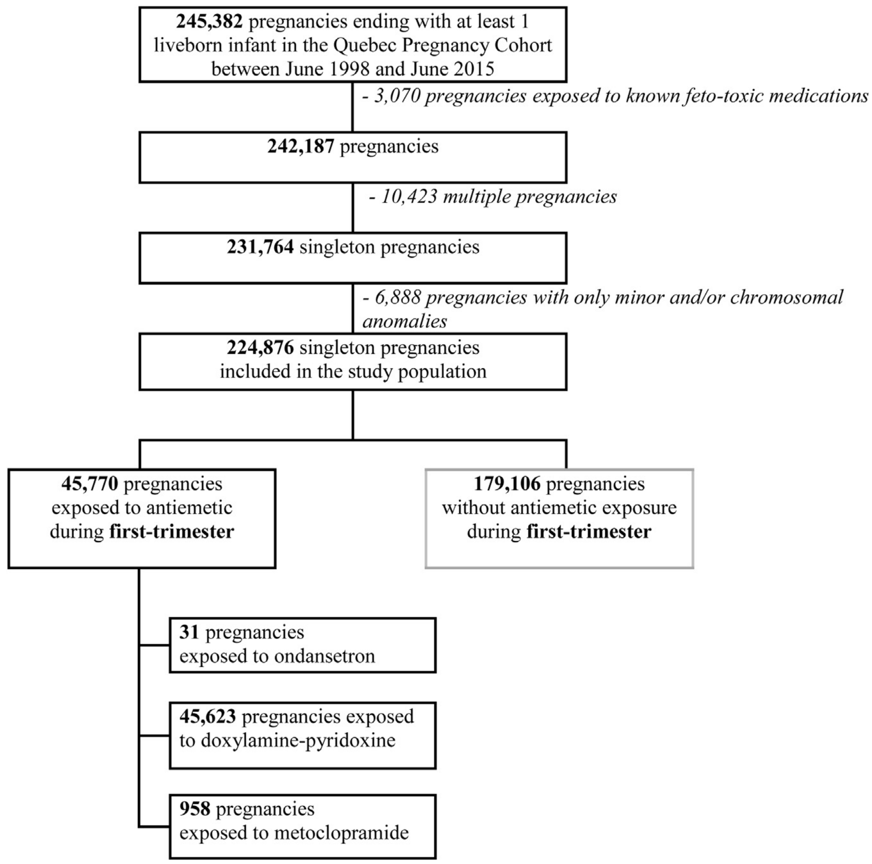

Fig. 1. Flowchart of cohort selection.

group (27.4 days) than for the metoclopramide exposed group (17.7 days) and the ondansetron exposed group (12.8 days).

Over the 17-year span of study, the prevalence of overall antiemetics use increased from 165.2 per 1,000 pregnancies to 290.8 per 1,000 pregnancies (76% increase; Cochran-Armitage Trend Test, $P < 0.0001$). This increasing use was observed for all three assessed antiemetics (Fig. 2).

Antiemetic users were younger, more likely to live in an urban area and be on welfare than nonusers (Table 1). Users had more comorbidities (i.e., hypertension, asthma, depression/anxiety/bipolar disorder, and epilepsy) and used more health services than nonusers. Users also had more diagnoses of tobacco addiction than nonusers; antibiotics use represented most other medication exposures in all three antiemetic study groups (59.2%). The high-dose periconceptional folic acid supplementation was similar among antiemetic users and nonusers. In terms of pregnancy-related outcomes, no differences between exposure groups were observed regarding birth weight and baby gender. However, users of antiemetics were more likely to have delivered preterm (Table 1). Table 2 presents the association between the use of each specific antiemetic medication during the first trimester and the risk of overall MCMs. When looking at the specific type of antiemetic used during the first trimester, doxylamine–pyridoxine and metoclopramide were statistically significantly associated with an increased risk of overall MCMs (aOR 1.07, 95% CI: 1.03–1.11; 3,945 exposed cases) and (aOR 1.27, 95% CI: 1.03–1.57; 105 exposed cases), respectively. Table 3 presents the crude and adjusted risks of organ-specific defects associated with the use of antiemetics during the first trimester. Doxylamine–pyridoxine exposure was statistically significantly associated with an increased risk of spina bifida (aOR 1.87, 95% CI: 1.11–3.14; 23 exposed cases), nervous system defects (aOR 1.25, 95% CI: 1.06–1.47; 225 exposed cases), and musculoskeletal system defects (aOR 1.08, 95% CI: 1.02–1.14; 1,735 exposed cases). Metoclopramide exposure was statistically associated with an increased risk of genital organ defects (aOR 2.26, 95% CI: 1.14–4.48; 10 exposed cases). Given the small number of exposed ondansetron pregnancies ($n = 31$), stratification on organ system resulted in multiple empty cells; thus, these pregnancies were excluded from Table 3. However, we know from Table 2 that among the 31 pregnancies exposed to ondansetron, two resulted in MCM (one congenital hydronephrosis and one other anomalies of the tongue).

NVP was not associated with the risk of MCM when taking into account the use of antiemetics, maternal sociodemographics, comorbidities, and health services utilization (Table 2). However, given that doxylamine–pyridoxine

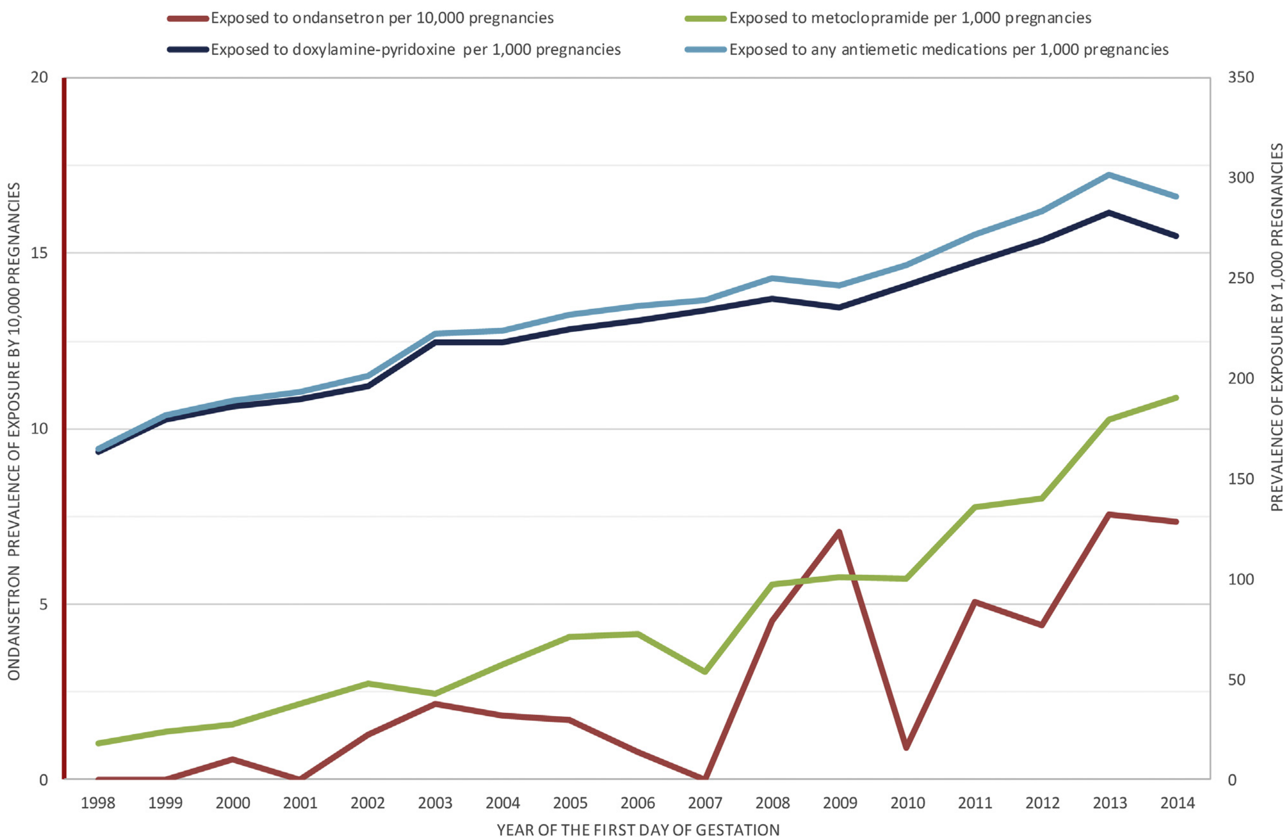

Fig. 2. Prevalence of antiemetic medication exposure during pregnancy, 1998–2015.

is given as first-line treatment followed by metoclopramide or ondansetron in more severe cases, and that doxylamine–pyridoxine can be given concomitantly with metoclopramide or ondansetron, we have performed an additional analysis within the subgroup of pregnant women with a diagnosis of NVP (Appendix Table S4). More than one different antiemetic (doxylamine–pyridoxine, metoclopramide, and ondansetron) during the first trimester of pregnancy was associated with a nonstatistically significant dose–response increase in the risk of MCM (Table S4), suggesting that severity of NVP has an impact on the risk of MCM.

4. Discussion

4.1. Main findings

Using the QPC, we found a 76% increase in the prevalence of antiemetics use during pregnancy over the 17-year study period. First-trimester doxylamine–pyridoxine and metoclopramide exposure were associated with an increased risk of overall MCMs. Doxylamine–pyridoxine exposure was associated with an increased risk of spina bifida, nervous system, and musculoskeletal system defects, whereas metoclopramide exposure was associated with an increased risk of genital organ defects. No association was found between first-trimester exposure to ondansetron and overall MCMs risk, although we only had 31 exposed pregnancies in our cohort, and caution is warranted.

4.2. Strengths and limitations

Our study used a population-based prospective pregnancy cohort with individual-level linkage of data, which allowed for the analysis of a large number of pregnancies with detailed information regarding exposure, outcomes, and potential confounders. Prescription fillings were used to determine medication exposure, which have been validated against maternal reports and showed high PPV and NPV for antiemetic exposure [22]. Our outcome (MCMs), gestational age, and medication timing of exposure have been validated [17,24].

Limitations include that because of the nature of our data, we did not have information on smoking status, low-dose over-the-counter (OTC) folic acid use, and alcohol intake. The periconceptional folic acid supplementation considered in our analyses only included high dose use (5 mg/d) because a prescription is required at this dosage level; we do not have data on OTC 1 mg/d exposure unless it is prescribed. However, based on our previous work [26,27], we hypothesize that the prevalence of use was similar between our study groups, leading to nondifferential misclassification. Furthermore, to minimize the

Table 1. Characteristics of the study population at the beginning of pregnancy

Variables	Unexposed (n = 179,106)	Antiemetic exposure during first trimester (n = 45,770)	P value[a]
Major congenital malformation			
Offspring	14,402 (8.0)	3,962 (8.7)	<0.001
Exposure during first trimester			
Ondansetron	NA	31 (0.01)	
Doxylamine-pyridoxine	NA	45,623 (20.3)	
Metoclopramide	NA	958 (0.4)	
Outpatient diagnosis of NVP during pregnancy	3,718 (2.1)	6,092 (13.3)	<0.001
Inpatient diagnosis of NVP during pregnancy	867 (0.5)	1,842 (4.0)	<0.001
Pregnancy related			
Gestational age (wk), mean (±SD)	38.9 ± 1.8	38.8 ± 1.8	0.10
Prematurity (<37 wk gestational age), n (%)	12,012 (6.7)	3,221 (7.0)	0.01
Birth weight (g), mean (±SD)	3,347.9 ± 539.6	3,348.6 ± 537.4	0.80
Low birth weight (<2,500 g), n (%)	9,194 (5.1)	2,295 (5.0)	0.30
Newborn gender (male), n (%)	91,981 (51.4)	23,354 (51.0)	0.21
Demographic characteristics at 1DG			
Maternal age, y, mean (±SD)	28.3 ± 5.6	27.7 ± 5.6	<0.001
Maternal age (y)			
<18	2,890 (1.6)	806 (1.8)	
18–34	148,248 (82.8)	38,816 (84.8)	
>35	27,968 (15.6)	6,148 (13.4)	<0.001
Urban dweller, n (%)	146,399 (81.7)	37,847 (82.7)	<0.001
Welfare recipient, n (%)	39,310 (22.0)	12,905 (28.2)	<0.001
Exposure to folic acid in 6 mo before 1DG and during first trimester	218 (0.1)	59 (0.1)	0.70
Maternal comorbidities in the year before 1DG			
Diabetes, n (%)	2,091 (1.2)	528 (1.2)	0.81
Hypertension, n (%)	3,067 (1.7)	890 (1.9)	<0.001
Asthma, n (%)		4,854 (10.6)	<0.001
Depression/anxiety/bipolar disorder	16,051 (9.0)	5,484 (12.0)	<0.001
Epilepsy, n (%)	710 (0.4)	276 (0.6)	<0.001
Obesity, n (%)	2,668 (1.5)	661 (1.4)	0.47
Tobacco dependence, n (%)	1,895 (1.1)	630 (1.4)	<0.001
Alcohol dependence, n (%)	256 (0.1)	70 (0.2)	0.62
Use of health services in the year before 1DG			
Visits to a general practitioner, mean (±SD)	3.0 ± 3.0	3.5 ± 5.8	<0.001
Visits to specialist physicians, mean (±SD)	2.4 ± 5.5	2.4 ± 5.5	0.03
At least one emergency department visit or hospitalization, n (%)	38,230 (21.3)	10,252 (22.4)	<0.001
No. of other prescribed medications use, mean (±SD)	1.4 ± 2.2	1.9 ± 2.7	<0.001
0	93,195 (52.0)	22,227 (48.6)	
1–2	45,970 (25.7)	10,144 (22.2)	
≥3	39,941 (22.3)	13,399 (29.3)	<0.001
Pregnancy follow-up by an obstetrician, n (%)	82,806 (46.2)	22,014 (48.1)	<0.001
Previous pregnancy in year before 1DG, n (%)	10,130 (5.7)	2,431 (5.3)	<0.001

Abbreviations: 1DG, first day of gestation; NA, not available; NVP, nausea and vomiting of pregnancy; SD, standard deviation.

[a] Compared with infants unexposed to antiemetics (ondansetron, doxylamine–pyridoxine, and metoclopramide) during the first trimester of pregnancy using t-test and χ^2 tests for continuous and categorical variables.

impact of the missing variables on smoking status and alcohol intake on our adjusted estimates, we took into account diagnoses of tobacco and alcohol dependence, which are both risk factors for MCM. Because the cohort only includes pregnant women insured by the Prescription Drug Insurance program, generalizability of results to those

Table 2. Association between use of antiemetic during first trimester and risk of major congenital malformation

			OR (95% CI)	
Exposure during first trimester	**Number of pregnancies**	**Number of MCM**	**Crude**	**Adjusted[a]**
Ondansetron	31	2 (6.5)	0.59 (0.14–2.57)	0.57 (0.13–2.49)
Doxylamine–pyridoxine	45,623	3,945 (8.7)	**1.08 (1.04–1.12)**	**1.07 (1.03–1.11)**
Metoclopramide	958	105 (11.0)	**1.33 (1.08–1.63)**	**1.27 (1.03–1.57)**
At least one diagnosis of NVP during pregnancy				
Outpatient diagnostic (yes/no)	9,810	874 (8.9)	**1.10 (1.02–1.18)**	1.04 (0.96–1.12)
Inpatient diagnostic (yes/no)	2,709	247 (9.1)	1.13 (0.99–1.29)	1.00 (0.86–1.16)
Demographic characteristics at 1DG				
Maternal age (y)	NA	NA	**1.00 (1.00–1.00)**	1.00 (0.99–1.00)
Welfare recipient (yes/no)	52,215	4,448 (8.5)	**1.06 (1.02–1.10)**	**1.05 (1.02–1.09)**
Urban dweller (yes/no)	40,630	3,071 (7.6)	**1.11 (1.06–1.15)**	**1.08 (1.04–1.13)**
Exposure to folic acid (≥5 mg/d) in 6 mo before 1DG and during first trimester	227	36 (13.0)	**1.67 (1.18–2.37)**	**1.68 (1.19–2.37)**
Maternal comorbidities in the year before 1DG				
Diabetes (yes/no)	2,619	279 (10.7)	**1.34 (1.18–1.52)**	**1.38 (1.22–1.57)**
Hypertension (yes/no)	3,957	359 (9.1)	**1.12 (1.00–1.25)**	**1.15 (1.03–1.29)**
Asthma (yes/no)	19,597	1,586 (8.1)	0.99 (0.93–1.04)	1.03 (0.97–1.09)
Depression/anxiety/bipolar disorder (yes/no)	21,535	1,751 (8.1)	0.99 (0.64–1.04)	1.05 (0.99–1.11)
Epilepsy (yes/no)	986	107 (10.9)	**1.36 (1.11–1.66)**	**1.42 (1.16–1.74)**
Obesity (yes/no)	3,329	257 (7.7)	**0.94 (0.82–1.07)**	0.96 (0.85–1.10)
Tobacco dependence (yes/no)	2,525	260 (10.3)	**1.29 (1.13–1.33)**	**1.29 (1.16–1.51)**
Alcohol dependence (yes/no)	326	28 (8.6)	**1.06 (0.72–1.56)**	1.10 (0.74–1.62)
Use of health services in the year before 1DG				
Emergency department visit or hospitalization (yes/no)	48,482	4,031 (8.3)	1.03 (0.99–1.07)	**1.13 (1.08–1.19)**
No. of general practitioner visits	NA	NA	0.99 (0.99–0.99)	0.99 (0.98–0.99)
No. of specialist physician visits	NA	NA	1.00 (0.99–1.00)	0.99 (0.99–1.00)
No. of other prescribed medication used[b]	NA	NA	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Pregnancy follow-up by an obstetrician (yes/no)	104,820	9,374 (8.9)	**1.21 (1.18–1.25)**	**1.21 (1.17–1.25)**
Previous pregnancy in year before 1DG (yes/no)	12,531	1,011 (8.1)	0.99 (0.92–1.05)	1.01 (0.94–1.08)

Abbreviations: 1DG, first day of gestation; CI, confidence interval; ED, emergency department; NA, not available; NVP, nausea and vomiting of pregnancy; OR, odds ratio.

Bold numbers signify statistically significant results.

[a] Adjusted for all the variables in this table.

[b] Other than antiemetic, or medication used to assess comorbidities.

insured by private drug insurance could be affected. However, validation studies have shown that pregnant women receiving medication coverage from Quebec's public insurance system are similar to those who are covered by private medication insurance in terms of comorbidity profiles and health care utilisation use [28]. Finally, the prevalence of MCMs in the QPC is higher than what is currently reported (9.8% vs. 3.5%) [29]. This is a known fact in the province of Quebec and is referred to as the Founder's effect [16,30]. Although our baseline prevalence of MCMs is high, it does not invalidate our study findings, given that the comparator groups have the same baseline prevalence of MCMs.

4.3. Interpretation

Our results on trends and patterns of antiemetic use were similar to those currently reported in the literature. In fact, a marked increase in antiemetic use, specifically ondansetron, has been observed in the US between 2001 and 2015 [10], whereas in Canada (British Columbia), use of doxylamine–pyridoxine has significantly increased between 2002 and 2011 [5]. Doxylamine–pyridoxine was removed from the US market in 1983 until 2013 [11]. This led to an increased use of ondansetron in the United States [10]. Meanwhile, doxylamine–pyridoxine remains recommended as the first-line treatment for NVP in Canada [2]. In our cohort, between 1998 and 2015, 20.3% (n = 45,623) of women used doxylamine–pyridoxine, 0.43% (n = 958) used metoclopramide, and 0.01% (n = 31) used ondansetron in their first trimester of pregnancy.

The meta-analysis cited in the Canadian guidelines was performed by Seto et al. [9] in 1997. They pooled 24 studies assessing the risk of MCMs with antihistamine exposure, which includes doxylamine [9]. Their results showed a

Table 3. Association between use of antiemetics during the first trimester and risk of organ system–specific congenital malformation

Malformation category	Number of pregnancies exposed (n = 45,739): Doxylamine–pyridoxine n = 45,598	Number of pregnancies exposed (n = 45,739): Metoclopramide n = 939	Nonexposed (n = 179,106)	Exposure group	Prevalence OR (95%CI): Crude	Prevalence OR (95%CI): Adjusted[a]
Overall major congenital malformations (number of cases: 18,362)	3,945 (8.65)	103 (10.97)	14,402 (8.04)	**Doxylamine–pyridoxine**	1.08 (1.04–1.12)	**1.07 (1.03–1.11)**
				Metoclopramide	1.32 (1.07–1.62)	**1.26 (1.02–1.56)**
Nervous system (number of cases: 892)	225 (0.49)	7 (0.75)	665 (0.37)	**Doxylamine–pyridoxine**	1.31 (1.13–1.53)	**1.25 (1.06–1.47)**
				Metoclopramide	1.59 (0.75–3.38)	1.26 (0.56–2.87)
Spina bifida (number of cases: 68)	23 (0.05)	1 (0.1)	45 (0.02)	**Doxylamine–pyridoxine**	1.97 (1.18–3.26)	**1.87 (1.11–3.14)**
				Metoclopramide	2.33 (0.32–17.10)	2.05 (0.23–17.92)
Eye, ear, face, and neck (number of cases: 725)	147 (0.32)	3 (0.32)	578 (0.32)	Doxylamine–pyridoxine	1.00 (0.83–1.20)	1.02 (0.84–1.22)
				Metoclopramide	0.99 (0.32–3.10)	0.98 (0.31–3.16)
Circulatory (including heart) system (number of cases: 4,529)	972 (2.13)	30 (3.19)	3,552 (1.98)	Doxylamine–pyridoxine	1.06 (0.99–1.14)	1.02 (0.95–1.11)
				Metoclopramide	1.54 (1.07–2.23)	1.39 (0.96–2.02)
Respiratory system (number of cases: 977)	219 (0.48)	7 (0.75)	755 (0.42)	Doxylamine–pyridoxine	1.12 (0.96–1.31)	1.07 (0.91–1.25)
				Metoclopramide	1.59 (0.74–3.42)	1.29 (0.57–2.91)
Digestive system (number of cases: 1,580)	369 (0.81)	11 (1.17)	1,210 (0.68)	Doxylamine–pyridoxine	1.19 (1.06–1.34)	1.12 (0.99–1.26)
				Metoclopramide	1.50 (0.82–2.74)	1.36 (0.71–2.59)
Genital organs (number of cases: 1,163)	232 (0.51)	10 (1.06)	930 (0.52)	Doxylamine–pyridoxine	0.96 (0.83–1.11)	0.98 (0.84–1.14)
				Metoclopramide	2.15 (1.15–4.03)	**2.26 (1.14–4.48)**
Urinary system (number of cases: 2,153)	433 (0.95)	8 (0.85)	1,719 (0.96)	Doxylamine–pyridoxine	0.99 (0.89–1.10)	1.02 (0.92–1.14)
				Metoclopramide	0.89 (0.44–1.80)	0.95 (0.47–1.92)
Musculoskeletal system (number of cases: 8,134)	1,735 (3.80)	39 (4.15)	6,393 (3.57)	**Doxylamine–pyridoxine**	1.07 (1.01–1.13)	**1.08 (1.02–1.14)**
				Metoclopramide	1.10 (0.79–1.52)	1.09 (0.78–1.52)

Abbreviations: CI, confidence interval; OR, odds ratio.

Bold numbers signify statistically significant results.

[a] Adjusted for maternal age on the first day of gestation (1DG); welfare status; urban dweller; emergency visit/hospitalization in the year before 1DG; outpatient and inpatient diagnosis of NVP; maternal comorbidities including obesity, hypertension, diabetes, asthma, epilepsy, and depression; folic acid exposure in the 6 months before the 1DG and during the first trimester; tobacco and alcohol dependence; number of general practitioner and specialist visits in the year before the 1DG, number of other prescribed medication during the current pregnancy; current pregnancy follow-up by an obstetrician, and prior pregnancy in the year before the 1DG.

protective effect (OR 0.76, 95% CI: 0.60–0.94), which is the basis of the current guideline recommendations [2,31]. However, Chin et al. [8] reanalyzed the same studies included in the previous meta-analysis and found a significantly increased risk of MCMs with first-trimester exposure to antihistamines (OR 1.09, 95% CI: 1.01–1.18; 774 exposed cases), whereas no significant association was found with first-trimester exposure to doxylamine alone (OR 1.07, 95% CI: 0.94–1.23; 338 exposed cases) [8].

In our population-based cohort study, we showed that first-trimester doxylamine–pyridoxine use was associated with an increased risk of overall MCM, spina bifida, nervous system defects, and musculoskeletal system defects. Our results are in line with the existing literature [14,32–34]. Using data from the National Birth Defects Prevention Study (NBDPS, 1997–2004), Anderka et al. [14] reported an increased risk of neural tube defects (aOR 1.84, 95% CI: 0.71–4.78; six exposed cases) with first-trimester doxylamine–pyridoxine exposure. Despite not being statistically significant because of a small number of exposed cases, the point estimate for the risk of neural tube defects is similar to ours [14]. In addition, Rothman et al. [32] found an increased risk of congenital heart defects (OR 1.8, 90% CI: 1.2–2.7; 24 exposed cases), and Aselton et al. [33] showed an increased risk of pyloric stenosis (OR 2.5, 95% CI: 1.2–5.2; 13 exposed cases) associated with first-trimester doxylamine–pyridoxine exposure. Eskenazi et al. [34] found that first-trimester doxylamine–pyridoxine use was associated with an increased risk of pyloric stenosis (OR 4.33, 95% CI: 1.75–10.75; six exposed cases), defective heart valves (OR 2.99, 95% CI: 1.02–8.74; four exposed cases), spina bifida (OR 2.99, 95% CI: 0.67–13.40; two exposed cases), cleft lip and palate (OR 2.21, 95% CI: 0.50−9.64; two exposed cases), and limb reduction (OR 4.19, 95% CI: 0.48−36.3; one exposed cases). More recently, Gilboa et al. [35] using data from the NBDPS reported increased risks of hypoplastic left heart syndrome, left ventricular outflow tract obstruction defects, spina bifida, and neural tube defects associated with first-trimester doxylamine exposure.

Doxylamine is an antihistamine that blocks histamine H1-receptor. As with any other H1 blocker, doxylamine possesses substantial antimuscarinic activity and may exhibit anticholinergic effects [36,37]. Eskenazi et al. [34] have proposed that faulty innervation of the abdominal viscera either by the vagus or the parasympathetic ganglia may be involved in the etiology of malformations.

Metoclopramide is the antiemetic drug of choice in pregnancy in European countries and Israel despite not being indicated for NVP [4]. Previous studies from Denmark [13,38], Israel [39], and Teratogen Information Centers [40,41] observed no significant association between first-trimester metoclopramide use and MCMs, which could partly be explained by the severity of NVP. Indeed, metoclopramide is the first-line treatment in Europe, whereas it is given for more severe NVP in Canada. The US NBDPS study aimed to examine specific birth defects and found no significant association with cleft palate in the offspring exposed to metoclopramide in the first trimester [14]. However, despite not being statistically significant because of a small number of exposed cases, the point estimate for the risk of cleft palate was high and suggested an increased risk (OR 2.36, 95% CI: 0.85−6.55; five exposed cases) [14].

In the British guidelines for NVP management, the maximum duration for metoclopramide therapy is 5 days [12]. Meanwhile, the Canadian [2] and US guidelines [42] do not report a maximum duration of exposure for this antiemetic. In the present study, the mean duration for metoclopramide use was 17.7 days, which is longer than previous studies assessing the risk of MCMs associated with metoclopramide exposure (13 days [13] in Denmark, 1 week [39], and 10 ± 10 days [40,41] in Israel).

4.4. Clinical implication

NVPs are prevalent and debilitating, and thus, treatment is needed and might include lifestyle changes. Although our results on the risk of MCM are consistent with other published studies, they require replications in further investigations. In addition, we did not look at the benefits of using such medications during pregnancy, and thus, women need to discuss the benefits/risks ratio with their health care providers to make an informed decision.

5. Conclusion

First-trimester doxylamine−pyridoxine and metoclopramide exposure were statistically significantly associated with an increased risk of overall MCMs. Although no association was found between first-trimester exposure to ondansetron and the risk of overall MCMs, caution is warranted given the few exposed pregnancies and thus the lack of statistical power. Our data may be used to guide clinicians in making an informed decision in the treatment of NVP during pregnancy.

CRediT authorship contribution statement

Anick Bérard: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing - original draft, Writing - review & editing. **Odile Sheehy:** Formal analysis, Writing - review & editing. **Jessica Gorgui:** Conceptualization, Writing - review & editing. **Jin-Ping Zhao:** Conceptualization, Writing - review & editing. **Cristiano Soares de Moura:** Conceptualization, Writing - review & editing. **Sasha Bernatsky:** Conceptualization, Writing - review & editing.

Supplementary data

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