Ondansetron use in early pregnancy and the risk of late pregnancy outcomes

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Abstract

Background: The effects of ondansetron, used off-label to treat nausea and vomiting during pregnancy, on common pregnancy complications are understudied. Modest effects of a commonly used drug could result in adverse events for large numbers of pregnant women. Therefore, our objective was to compare the risk of stillbirth, preterm birth, gestational hypertensive disorders, small for gestational age, and differences in birth weight between women prescribed ondansetron and women prescribed alternative antiemetics in early pregnancy.

Methods: A cohort of pregnant women receiving a prescription for ondansetron or comparator antiemetics (metoclopramide or promethazine) during the first 20 weeks of pregnancy was identified using electronic health record data from a health care system in North Carolina, USA. Confounding by multiple covariates was controlled using stabilized inverse probability of treatment weights. Weighted hazard ratios (HR) and 95% confidence intervals (CI) accounted for competing events.

Results: We identified 2677 eligible pregnancies with antiemetic orders, 66% for ondansetron. The small number of stillbirths (n = 15) resulted in an imprecise estimate of the association with ondansetron (HR = 1.60; 95%CI 0.51, 4.97). No association was observed for preterm birth (HR = 0.90; 95%CI 0.67, 1.20) or gestational hypertensive disorders (HR = 0.87; 95%CI 0.68, 1.12). We observed an association with small for gestational age (HR = 1.37; 95%CI 0.98, 1.90), however mean birth weight among term births was similar between groups.

Conclusions: Our results do not suggest that ondansetron increases the risk of preterm birth or gestational hypertensive disorders. The weak association observed between ondansetron use and small for gestational age warrants further investigation.

KEYWORDS
electronic health records, nausea and vomiting, ondansetron, pharmacoepidemiology, pregnancy, pregnancy complications

1 | INTRODUCTION

Ondansetron, a 5-HT_3 receptor antagonist, is approved by the Food and Drug Administration (FDA) for treating chemotherapy-induced

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and post-surgical nausea and vomiting. It is not FDA approved for use during pregnancy but is often prescribed off-label and is recommended for severe cases by the American College of Obstetricians and Gynecologists.[1] More than 20% of pregnant women were estimated to have filled a prescription for ondansetron in the United States in 2014.[2] With increasing use in the United States, the safety of ondansetron use in pregnancy for nausea and vomiting is a topic of interest.[2] Numerous studies have focused on the risk of birth defects and conflicting results have been published regarding the risk of cardiac and orofacial cleft defects.[3-7] Less attention has been paid to other pregnancy outcomes, including common but less serious adverse outcomes such as preterm birth, low birth weight, and hypertensive disorders, or rare and serious outcomes including stillbirth. The few studies evaluating these adverse outcomes in association with ondansetron use have compared women using ondansetron to a general population of pregnant women not using ondansetron,[8,9] and have not otherwise appropriately controlled for confounding.[8] Use of a comparator group composed of women taking similar drugs for the same indication of nausea and vomiting during pregnancy, called an active comparator, helps to control for confounding by comparing groups of women with similar symptom severity.[10] Additionally, this comparison helps inform treatment decisions for women requiring symptom relief.

As nausea and vomiting are symptoms experienced by nearly 80% of women during early pregnancy,[11] modest effects on common outcomes could result in adverse outcomes for large numbers of pregnant women every year. Therefore, the objective of this study was to add to the limited literature on the effect of ondansetron use on stillbirth, preterm birth, birth weight, and hypertensive disorders by comparing the risk of these outcomes between women using ondansetron and women using alternative antiemetic medications that are commonly used off-label in pregnancy in the United States, promethazine and metoclopramide.

KEY POINTS

- While numerous studies have evaluated the risk of birth defects following ondansetron exposure, few have included common or serious outcomes including stillbirth, preterm birth, gestational hypertensive disorders, or small for gestational age.
- Use of electronic health records as the data source allowed for use of clinical gestational age estimates and inclusion of inpatient and emergency room administrations of antiemetic drugs.
- Use of an active comparator of similarly prescribed antiemetics helped to control for confounding by nausea and vomiting symptoms by design.
- The results do not suggest that ondansetron increases the risk of preterm birth or gestational hypertensive disorders.
- The weak association observed between ondansetron use and small for gestational age warrants further investigation.

2 | METHODS

2.1 | Data source

The study cohort was created using electronic health record (EHR) data from the University of North Carolina (UNC) Health Care system. UNC Health Care is a state-owned, non-profit health care system in North Carolina comprised of the academic medical campus at UNC Medical Center, 11 affiliate hospital systems, and affiliate provider networks across the state. Starting in April 2014, UNC Health Care adopted the Epic (Verona, WI) EHR system to standardize records across the system. We used all encounters, diagnosis, procedures, and medication orders in the Epic system from April 2014 through November 2017. This study was approved by the UNC Institutional Review Board.

2.2 | Identifying pregnancies

Pregnancies were defined by identifying the first clinical encounter with recognition of pregnancy based on diagnosis and procedure codes that are expected to occur in the first half of pregnancy (codes listed in the supplemental materials), or the initiation of a pregnancy event in the Epic EHR system. Pregnancies were followed forward from this index date until evidence of a pregnancy outcome. If no outcome was identified, pregnancies were considered lost to follow-up as of the last visit with evidence of an active pregnancy; this included pregnancies that were not fully observed because of the end of the study period on November 30, 2017. Gestational age was defined using physician recorded gestational age, which was derived using last menstrual period dates or ultrasound. For pregnancies without gestational age recorded in standardized fields, ICD-9 and ICD-10 codes indicating specific gestational weeks were used to classify gestational age, and medical record abstraction for last menstrual period or expected date of delivery was completed for pregnancies without these codes. Multiple pregnancies could be identified for a single woman. We excluded ectopic and molar pregnancies. Additionally, multiple gestation pregnancies were excluded. If a pregnancy was first identified after reaching 20 weeks of gestation, it was excluded from the analysis because exposure status before 20 weeks could not be assessed. A detailed description of the process for defining pregnancies, including all diagnosis and procedure codes used to define pregnancies and outcomes, is included in the supplemental materials (section A).

2.3 | Antiemetic exposure

Antiemetic exposure was defined using prescription orders. Women with orders for ondansetron, promethazine, or metoclopramide

between gestational weeks 2 (conception) and 20 were eligible for the analysis. Exposure groups were defined by the first prescription of the three eligible antiemetics received during pregnancy (main group: ondansetron, comparator group: promethazine or metoclopramide). Promethazine and metoclopramide were chosen as comparators because, similar to ondansetron, they are recommended for use in moderate cases when diet and over-the-counter options have failed.[1] These drugs have historically been widely used during pregnancy in the United States,[2,12] however recently have decreased in use due to the availability of ondansetron in generic form and its more favorable side effect profile.[2,13] Women who received prescriptions for antiemetics from both exposure groups on the day of their first eligible antiemetic prescription were excluded because exposure groups could not be classified for these women.

Medications were classified by the care setting in which they were ordered (an outpatient, inpatient, or emergency encounter) and the type of prescription order (written or administered). Written prescriptions were given to a patient to be filled at a pharmacy outside of the health care setting and self-administered; information on whether the prescription was filled by the patient was not available. Administered prescriptions included all medications taken by the patient in a health care facility, including intravenous (IV) medications. We refer to medications taken in a healthcare setting as "administered" instead of "filled" because they were taken while under supervision in a healthcare facility and not filled for self-administration. We determined indications for antiemetic orders using diagnosis and procedure codes on the date of antiemetic order or within one day prior to the order. Indications included nausea and vomiting of pregnancy, inpatient diagnosis of hyperemesis gravidarum (HEG), a surgical procedure, and chemotherapy or radiation therapy.

2.4 | Outcome definitions

Stillbirth was defined as intrauterine fetal demise after 20 weeks of gestation. Potential stillbirth cases were identified using diagnosis and procedure codes, and medical records for all cases were reviewed to confirm the outcome types.

Preterm birth was defined using gestational age at birth. Live births with a gestational age of 258 days or less (<37 weeks) were classified as preterm. Early preterm status was defined by live births with a gestational age of 237 days or less (<34 weeks).

Birth weight was based on delivery records. Small for gestational age status was defined using the 10th percentile of birth weights by gestational week of birth using the birth weight distribution for the United States in the year 2000.[14] The most appropriate method for studying low birth weight as an adverse pregnancy outcome is controversial,[15,16] therefore differences in the birth weight distribution among term live births and low birth weight, defined as birth weight less than 2500 g, were also examined between antiemetic groups.

Gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome were categorized together into a general category of *gestational hypertensive disorders*. Cases were included if they received a diagnosis code for one of these conditions during an inpatient encounter between 20 weeks of gestation and delivery. Use of inpatient diagnosis codes to identify preeclampsia had high positive predictive value of 91% or above in Medicaid data and hospital discharge data.[17,18]

All diagnosis codes used to define outcomes are listed in Supplement A.

2.5 | Covariates

Maternal age was defined at the start of pregnancy. Race and ethnicity were classified as white, black, and other, consisting of Asian, American Indian or Alaska Native, Native Hawaiian, other Pacific Islander, or report of "other race". Insurance status was defined by the payment type used at the encounter of the first eligible antiemetic order (public, private, self-pay). Smoking status was defined using encounter data for the period between pregnancy start and the first eligible antiemetic order (current, former, or never use).

Proxy measures for nausea and vomiting severity included hospitalization or emergency room visits for HEG, the care setting for first eligible antiemetic order, the administration method of the antiemetic, and prescription orders for antiemetics other than ondansetron, metoclopramide, and promethazine (doxylamine/pyridoxine, antihistamines and dopamine antagonists other than promethazine and metoclopramide, and scopolamine patches). Comorbidities were defined using diagnosis and procedure codes in the record on or prior to the date of first eligible antiemetic order and included asthma, renal disease, depression, other mental health disorders, diabetes, seizure disorders, alcohol abuse, and drug abuse. Concomitant medication use was defined as an inpatient administered prescription between the start of pregnancy and the date of the first eligible antiemetic order, or an outpatient prescription within 60 days prior to the first eligible antiemetic order, and included analgesics, anticonvulsants, antipsychotics, benzodiazepines, nonsteroidal anti-inflammatory drugs, antidepressants, proton-pump inhibitors, antihypertensives, insulin, and opioids. Prenatal vitamin orders were included from 60 days prior to pregnancy start until the first eligible antiemetic order. Health care utilization in early pregnancy was measured based on having at least one emergency room, inpatient, or outpatient visit at a UNC Health Care facility at or prior to the first eligible antiemetic order. Prepregnancy body mass index (BMI) was extracted from the pregnancy record; when this was missing, height and weight measurements from one year prior to pregnancy start through 10 weeks of gestation were collected and the most recent measurements were used to calculate BMI.

2.5.1 | Statistical analysis

The cause-specific cumulative incidences of stillbirth, preterm birth, small for gestational age status, and gestational hypertensive

disorders were estimated separately in each antiemetic group accounting for competing events and varied entry times.[19,20] Women were followed from the gestational age of first eligible antiemetic prescription until the event of interest, loss to follow-up, or until they are no longer at risk for the outcome (considered a competing event). Miscarriage and termination of pregnancy were considered competing events for all outcomes. Cumulative incidence was calculated at the end of the risk period for each outcome, as detailed in Figure 1. The main analysis followed an intent-to-treat design and changes in antiemetic prescribing after the first prescription were ignored. This analysis accounts for all events that occur after exposure and therefore estimates the unconditional risk of the study outcomes.[21]

Differences in the birth weight distribution among term births (37-42 weeks) between antiemetic groups were analyzed by comparing mean birth weight using linear regression given the normal distribution of birth weight among term births. Risk ratios were also calculated for low birth weight, defined as birth weight less than 2500 g, among live-born infants.

Missing data for race (1.3%), ethnicity (1.9%), smoking status (1.9%), pre-pregnancy BMI (12.0%), and birth weight (1.0%) were imputed using multiple imputation with chained equations (MICE) using five imputed datasets.[22] A comparison of the observed and imputed data is presented in the supplemental materials (Table S1 and Figure S1). Measured confounding was controlled using stabilized inverse probability of treatment weights.[23] Propensity scores were estimated with multivariable logistic regression. To minimize the impact of large weights due to women being treated contrary to prediction, we applied asymmetric trimming of the propensity score using the 1st and 99th percentiles and re-estimated the propensity score in the trimmed population.[24] We planned to estimate associations between antiemetic use and the outcomes of interest by calculating risk differences and risk ratios from weighted cumulative incidence estimates. This method requires use of bootstrapping to estimate 95% confidence intervals.[25] However, empirical confidence intervals resulting from the bootstrap were wide and unstable (results are presented in the supplemental materials, Table B3, for the main analysis). Therefore, we alternatively used the Fine-Gray subdistribution hazard model to estimate subdistribution hazard ratios (HR) to account for competing events.[20] Exposure was defined as time-varying to account for the gestational age of first eligible antiemetic order, and measured confounding was adjusted using IPT-weighted models. Violation of the proportional hazards assumption was checked using an interaction term between time and the exposure in the model. 95% confidence intervals were calculated using a robust variance to account for the IPT-weighting and the inclusion of multiple pregnancies per woman.

Analyses were completed in R version 3.5.3 using the *mice*, *mstate*, *survival*, and *boot* packages.[26-29]

2.6 | Per-protocol analysis

Women may receive prescriptions for different antiemetics if their first prescription does not achieve symptom control; this will result in

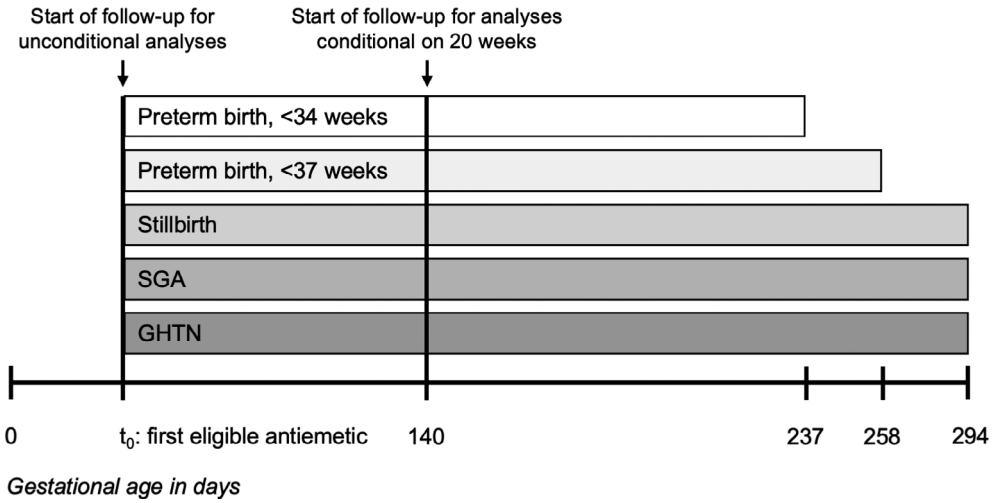

FIGURE 1 Period of cumulative incidence estimation for all outcomes. The bars indicate at-risk periods for all outcomes. Cumulative incidence was estimated at the end of the at-risk period. For unconditional analyses, follow-up started at t_0, the gestational age of the first eligible antiemetic order. For analyses conditional on 20 weeks, a woman entered the analysis at the start of 21 weeks, or 141 days. Women remained in the risk set for the outcome until the gestational age of the outcome, censoring due to loss to follow-up, or end of the risk period. In unconditional analyses, miscarriage and termination were competing events for all outcomes. For the preterm birth analysis, pregnancies were administratively censored at the end of the preterm period. All other pregnancy outcomes that resulted in the pregnancy being no longer at risk for the outcome of interest were treated as competing events. For preterm birth outcomes, stillbirth was a competing event. For the stillbirth analysis, live birth was a competing event. For the small for gestational age and gestational hypertensive disorders analyses, stillbirth and live birth without the outcome of interest were competing events. Abbreviation: GHTN, gestational hypertensive disorders; SGA, small for gestational age

misclassification of exposure status when exposure is defined by the first eligible antiemetic received. Therefore, an analysis was performed in which women with prescriptions for both antiemetic groups in the first 20 weeks of pregnancy were censored at the gestational age of the prescription for their second antiemetic type.[30]

2.7 | Sensitivity analyses

To address exposure misclassification due to lack of antiemetic consumption, we completed analyses limiting antiemetic exposure groups to those with administered medications, including IV administrations and inpatient administrations (administered analysis). Analyses were also completed restricting to a cohort of women with at least one prenatal care visit in the UNC record in the first 20 weeks of pregnancy to limit the impact of missing data (prenatal care analysis). This population excludes women who sought emergency care for nausea and vomiting and deliver at a UNC Health Care facility but may have received prenatal care elsewhere. The prenatal care analysis was restricted to women whose pregnancies continued until the start of 21st week to avoid inclusion of immortal time between the first eligible antiemetic order and the first prenatal care visit.[31] Restricting to women whose pregnancies survived until the start of the 21st week estimates conditional risk because it excludes competing events of miscarriage and termination that occur after exposure but before the 21st week. If the risk of miscarriage or termination differs between antiemetic exposure groups, contrasts of conditional risk estimates can be biased.[21] Therefore, we also estimated conditional results, without restriction to pregnancies with prenatal care, to facilitate comparison of the main results to results from the prenatal care sensitivity analysis. The timeline for conditional analyses is detailed in Figure 1.

3 | RESULTS

We identified 3241 pregnant women with orders for ondansetron, promethazine, or metoclopramide between gestational weeks 2 and 20. Examination of indications for each antiemetic group revealed a large imbalance in receipt of antiemetics after surgical procedure or chemotherapy (N = 103 in ondansetron group, N = 8 in comparator group). Women with these indications were excluded from the analysis, as were women with orders of ondansetron and comparators on the same day, multiple gestations, and ectopic or molar pregnancies. 1742 ondansetron exposed and 935 comparator exposed women remained in the analysis population (Figure 2). Loss to follow-up was similar in both groups, accounting for 29% of ondansetron exposed women and 36% of comparator exposed women. Descriptive characteristics for women lost to follow-up and not lost to follow-up are presented in Table B2 of the supplemental materials. Women lost to follow-up were slightly younger, more likely to be on public insurance, more likely to be smokers, and more likely to appear in the emergency room than women not lost to follow-up.

Few differences were observed in patient characteristics between antiemetic exposure groups (Table 1). Comparator antiemetics were more likely than ondansetron to be initiated intravenously and/or in an emergency room setting. The median gestational age at first eligible antiemetic order was 63 days (interquartile range: 50-86) in the ondansetron group and 67 days (interquartile range: 50-89) in the comparator group. Women in the comparator group were also more likely to receive orders for antiemetics other than ondansetron, promethazine, and metoclopramide. Hospitalization for HEG at the time of first eligible antiemetic prescription was rare in both groups (less than 2%) and emergency room visits for HEG were similar between groups (16% among ondansetron exposed, 19% among comparator exposed). After propensity score weighting, groups were similar on all variables

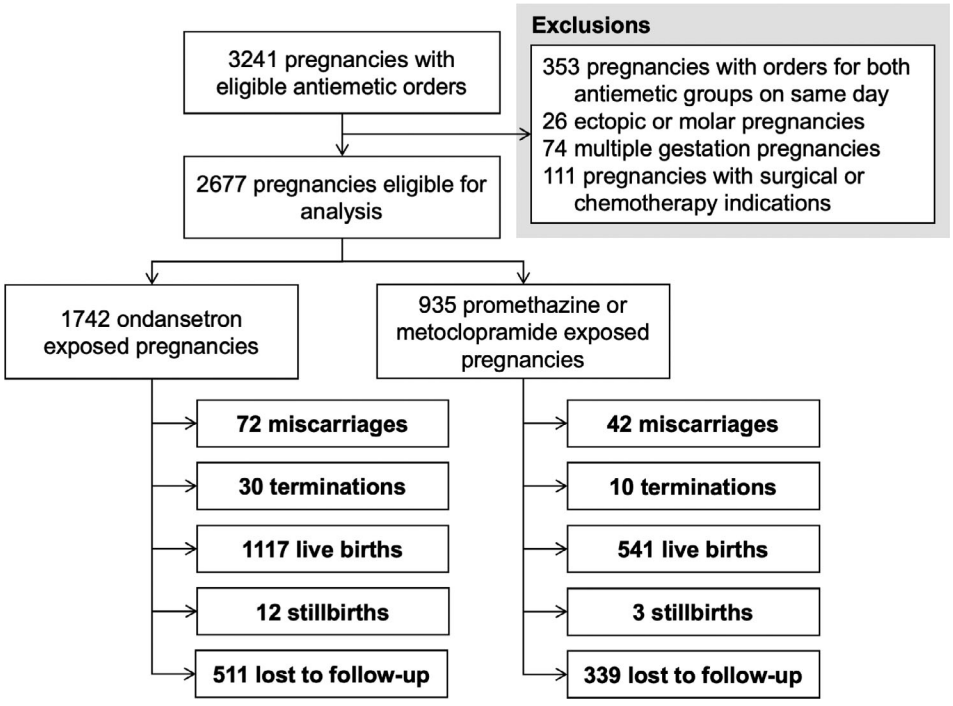

FIGURE 2 Inclusion and exclusion of pregnancies in the analysis

TABLE 1 Characteristics of pregnant women seen at UNC Health Care between 2014-2017 with antiemetic exposure by antiemetic exposure status

	Unweighted			IPT-Weighted
	Ondansetron (N = 1742)	Comparators (N = 935)	Absolute standardized difference	Absolute standardized difference
Age in years at start of pregnancy, mean (SD)	27.5 (5.9)	27.4 (5.8)	0.02	0.00
Insurance status				
Private insurance	728 (41.8)	353 (37.8)	0.08	0.01
Public insurance	722 (41.4)	420 (44.9)	0.07	0.01
No insurance	292 (16.8)	162 (17.3)	0.02	0.01
Race				
White or Caucasian	832 (47.8)	436 (46.6)	0.02	0.00
Black or African American	540 (31.0)	319 (34.1)	0.07	0.01
Other	348 (20.0)	167 (17.9)	0.05	0.01
Missing	22 (1.3)	13 (1.4)		
Hispanic	263 (15.1)	127 (13.6)	0.04	0.01
Missing	33 (1.9)	17 (1.8)		
Smoking status				
Current smoker	370 (21.2)	213 (22.8)	0.04	0.00
Former smoker	228 (13.1)	135 (14.4)	0.04	0.01
Never smoker	1110 (63.7)	570 (61.0)	0.06	0.00
Missing	34 (2.0)	17 (1.8)		
Comorbidities				
Asthma	118 (6.8)	82 (8.8)	0.08	0.01
Renal disease	25 (1.4)	17 (1.8)	0.03	0.04
Depression	230 (13.2)	123 (13.2)	0.00	0.02
Other mental health disorders	250 (14.4)	135 (14.4)	0.00	0.00
Hypertension	120 (6.9)	89 (9.5)	0.10	0.01
Sleep disorders	37 (2.1)	19 (2.0)	0.01	0.01
Diabetes	48 (2.8)	36 (3.9)	0.06	0.01
Seizure disorders	38 (2.2)	25 (2.7)	0.03	0.01
Alcohol abuse	10 (0.6)	8 (0.9)	0.03	0.02
Drug abuse	94 (5.4)	59 (6.3)	0.04	0.01
High risk pregnancy	295 (16.9)	163 (17.4)	0.01	0.01
Pre-pregnancy body mass index				
Underweight or normal (<24.9)	656 (37.7)	298 (31.9)	0.07	0.01
Overweight (25 to <30)	381 (21.9)	203 (21.7)	0.03	0.01
Obese (30 or greater)	526 (30.2)	290 (31.0)	0.04	0.01
Missing	179 (10.3)	144 (15.4)		
Concomitant medications				
Prenatal vitamins	253 (14.5)	163 (17.4)	0.08	0.00
Analgesics	496 (28.5)	274 (29.3)	0.02	0.01
Anticonvulsants	25 (1.4)	22 (2.4)	0.07	0.01
Antipsychotics	24 (1.4)	24 (2.6)	0.09	0.02
Benzodiazepines	28 (1.6)	21 (2.2)	0.05	0.01
Nonsteroidal anti-inflammatory drugs	133 (7.6)	57 (6.1)	0.06	0.01
Antidepressants	82 (4.7)	35 (3.7)	0.05	0.03
Proton-pump inhibitors	48 (2.8)	23 (2.5)	0.02	0.02

(Continues)

TABLE 1 (Continued)

	Unweighted			IPT-Weighted
	Ondansetron (N = 1742)	Comparators (N = 935)	Absolute standardized difference	Absolute standardized difference
Antihypertensives	20 (1.1)	16 (1.7)	0.05	0.03
Insulin	16 (0.9)	14 (1.5)	0.05	0.00
Opioid	253 (14.5)	139 (14.9)	0.01	0.01
Health care utilization at UNC, % with 1 or more visits at or before antiemetic order				
Emergency room visit	900 (51.7)	543 (58.1)	0.13	0.02
Inpatient visit	124 (7.1)	51 (5.5)	0.07	0.01
Outpatient visit	1054 (60.5)	510 (54.5)	0.12	0.01
Pregnancy-related care at or before antiemetic order				
Prenatal care visit	721 (41.4)	355 (38.0)	0.07	0.02
Maternal/fetal medicine (high-risk) visit	236 (13.5)	147 (15.7)	0.06	0.01
UNC Health Care System hospital of antiemetic order				
Caldwell, Chatham, Lenoir, or Pardee	151 (8.7)	84 (9.0)	0.01	0.00
High Point Regional	237 (13.6)	128 (13.7)	0.00	0.01
Johnston	128 (7.3)	118 (12.6)	0.18	0.01
Rex	182 (10.4)	213 (22.8)	0.34	0.02
UNC Hospitals	1044 (59.9)	392 (41.9)	0.37	0.01
Year				
2014	404 (23.2)	75 (8.0)	0.43	0.33
2015	423 (24.3)	158 (16.9)	0.18	0.13
2016	520 (29.9)	388 (41.5)	0.25	0.18
2017	395 (22.7)	314 (33.6)	0.24	0.18
Gestational age at order, median (interquartile range)	**63 (50, 86)**	**67 (50, 89)**		
Care setting of antiemetic order				
Emergency	761 (43.7)	487 (52.1)	0.17	0.03
Inpatient	116 (6.7)	49 (5.2)	0.06	0.01
Outpatient	865 (49.7)	399 (42.7)	0.14	0.02
Administration of antiemetic				
Inpatient administration	745 (42.8)	442 (47.3)	0.09	0.04
IV administration	443 (25.4)	380 (40.6)	0.33	0.04
Orders for other antiemetics[a]	238 (13.7)	267 (28.6)	0.37	0.04
Indications for antiemetics				
Nausea and vomiting	565 (32.4)	374 (40.0)	0.16	0.03
Hyperemesis gravidarum (inpatient)	23 (1.3)	15 (1.6)	0.02	0.01
Hyperemesis gravidarum (emergency)	285 (16.4)	181 (19.4)	0.08	0.03

Abbreviations: IPT, inverse probability of treatment; IV, intravenous; UNC, university of North Carolina.
[a]Other antiemetics included doxylamine/pyridoxine, antihistamines and dopamine antagonists other than promethazine and metoclopramide, and scopolamine patches.

included in the propensity score with absolute standardized mean differences less than 10%.[32]

3.1 | Main results

Results from the intent-to-treat style analysis are presented in Table 2. The risk of stillbirth was 0.8% (n = 12) in the ondansetron group and 0.4% (n = 3) in the comparator group (crude HR 1.82, 95% CI 0.51, 6.48). After weighting, the association between stillbirth and ondansetron was attenuated (HR 1.60, 95% CI 0.51, 4.97) but imprecise with a confidence limit ratio near 10. The risk of preterm birth was 8.5% in the ondansetron group and 9.6% in the comparator group. The weighted HR indicated no association between antiemetic use and preterm birth (HR 0.90, 95% CI 0.67, 1.20), and a weak inverse association for early preterm birth before 34 weeks (HR 0.76,

TABLE 2 Risk of late pregnancy outcomes and hazard ratios among pregnant women seen at UNC Health Care between 2014 and 2017 with ondansetron or comparator antiemetic exposure

		Unweighted cumulative incidence[a] (%)		Unweighted		IPT-weighted	
	N cases / N total	Estimate	95% CI	HR	95% CI	HR	95% CI
Stillbirth							
Ondansetron	12 / 1742	0.8%	0.1, 2.2	1.82	0.51, 6.48	1.60	0.51, 4.97
Comparators	3 / 935	0.4%	0, 1.5	1		1	
Preterm birth, <37 weeks							
Ondansetron	125 / 1742	8.5%	5.0, 12.8	0.88	0.65, 1.18	0.90	0.67, 1.20
Comparators	67 / 935	9.6%	4.8, 16.5	1		1	
Preterm birth, <34 weeks							
Ondansetron	35 / 1742	2.3%	0.9, 4.7	0.75	0.44, 1.26	0.76	0.46, 1.23
Comparators	22 / 935	3.1%	0.8, 7.4	1		1	
Hypertensive disorders							
Ondansetron	177 / 1742	12.6%	8.0, 17.7	0.76	0.60, 0.96	0.87	0.68, 1.12
Comparators	107 / 935	15.9%	9.4, 24.0	1		1	
Small for gestational age							
Ondansetron	148 / 1742	8.0%	4.8, 12.1	1.42	1.05, 1.91	1.37	0.98, 1.90
Comparators	64 / 935	6.1%	2.6, 10.5	1		1	

Abbreviations: CI, confidence interval; HR, hazard ratio; UNC, University of North Carolina.
[a]Crude cumulative incidence estimated using the Fine and Gray estimator accounting for competing events and left truncation.

95% CI 0.46, 1.23). The risk of gestational hypertensive disorders was lower in the ondansetron group than the comparator group (12.6% and 15.9%, respectively), however this was attenuated after covariate weighting (HR 0.87, 95% CI 0.68, 1.12). Risk of having an SGA infant was higher in the ondansetron group, and the weighted HR suggested a positive association between SGA and ondansetron use (8.0% in the ondansetron group, 6.1% in the comparator group; weighted HR 1.37, 95% 0.98, 1.90).

Per-protocol analysis and other sensitivity analyses.

Results of the per-protocol analysis and other sensitivity analyses are presented in Figure 3. Sixteen percent (n = 285) of women in the ondansetron group and 18% (n = 169) of women in the comparator group had a subsequent prescription for an antiemetic in the other exposure group; accordingly, in the per-protocol analysis, follow-up was censored at the gestational age of this second antiemetic prescription. The administered population included 745 ondansetron and 442 comparator exposed women, and the prenatal care population included 954 ondansetron and 407 comparator exposed women. Results from the analysis conditional on survival until the 21st week of gestation were very similar to the main results (conditional results are presented in Supplemental Table B4), therefore direct comparisons of the prenatal care sensitivity analyses to the main results are justified. Results across the per-protocol, administered, and prenatal care analyses were consistent for preterm birth and gestational hypertensive disorders, but showed more variability for other outcomes. Both the per-protocol analysis and the administered analysis suggest strong inverse association between ondansetron use and early preterm birth. Results from the per-protocol analysis and the prenatal care analysis agree with an increase in risk of having an SGA infant in the ondansetron group. Sensitivity analyses were not completed for stillbirth due to the small number of cases.

3.2 | Birth weight analyses

Results from linear regression analyses comparing birth weight distributions among term live births are presented in Table 3. No difference in mean birth weight was observed in the main analysis or in the per-protocol and prenatal care sensitivity analyses. In the administered analysis, mean birth weight was 78 g lower in the ondansetron group. Weighted risk ratios for low birth weight similarly showed no increase in risk for low birth weight among ondansetron exposed women and results were consistent across sensitivity analyses (Supplemental Table B5).

4 | DISCUSSION

In this analysis of women with prescriptions for ondansetron or comparator antiemetics in the UNC Health Care system, we observed no clinically meaningful differences in the risk of preterm birth or gestational hypertensive disorders. While the risk of early preterm birth (<34 weeks) was lower in the ondansetron group, small numbers of cases resulted in wide confidence intervals limiting our ability to conclude a difference in risk. Results for having an SGA infant may be suggestive of an increased risk among ondansetron users, however

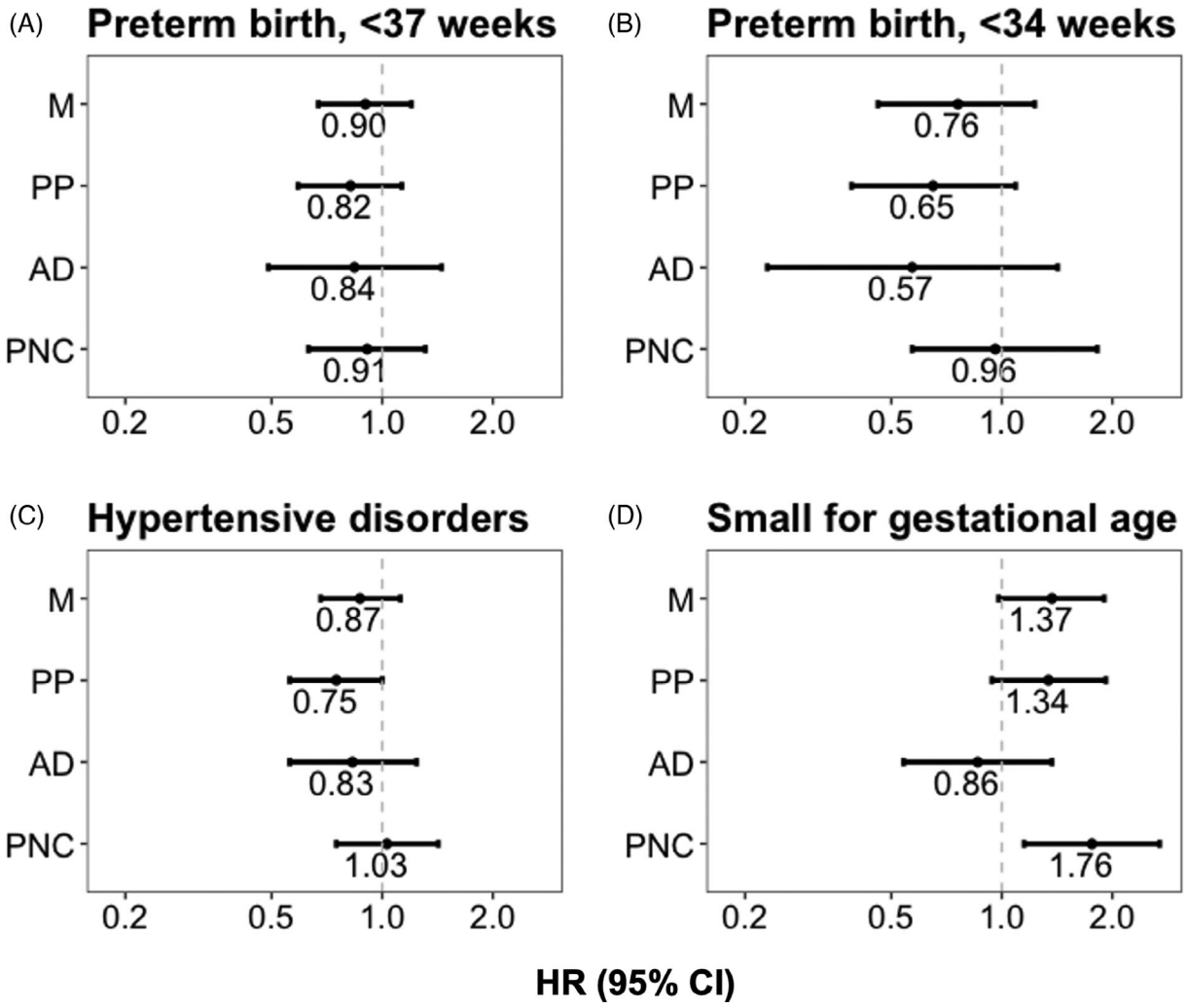

FIGURE 3 Association of late pregnancy outcomes among pregnant women seen at UNC Health Care between 2014 and 2017 with ondansetron or comparator antiemetic exposure in sensitivity analyses. Hazard ratios and 95% confidence intervals for the results of the main analysis and sensitivity analyses for, A, preterm birth, B, early preterm birth, C, gestational hypertensive disorders, and, D small for gestational age. AD, administered analysis; M, main analysis; PNC, prenatal care analysis; PP, per-protocol analysis

examination of birth weight among term live births did not reveal clinically significant differences in mean birth weight between ondansetron users and comparator antiemetic users. An elevated risk of stillbirth among ondansetron users was not definitive due to the very small number of cases in the comparator antiemetic group.

To minimize exposure and covariate misclassification due to receiving pregnancy care at other institutions, we performed a sensitivity analysis restricted to women with prenatal care at a UNC Health Care facility in the first 20 weeks of pregnancy. This sensitivity analysis resulted in HRs closer to the null for all outcomes except SGA. This restriction also excludes women who primarily receive care through emergency room visits in the first half of pregnancy. It is possible that results in the prenatal care population are less vulnerable to unmeasured confounding than the primary results due to the higher likelihood of observing all pregnancy related care in this population.

EHR data are limited by a lack of data on prescription fills or consumption. The per-protocol and administered sensitivity analyses aimed to limit the potential for exposure misclassification due to this limitation. The per-protocol results, which censored women if they had a prescription for the comparator antiemetic in the first 20 weeks of pregnancy, were largely consistent with the main results. The administered results, which defined antiemetic use as having the medication administered in a healthcare facility, were variable. This restriction resulted in a small population of women with high utilization of emergency services and a high proportion of HEG diagnoses compared to the full or prenatal care populations. Therefore, results from this sub-population may minimize exposure misclassification but also represent a less generalizable population of women. Additionally, these estimates may be more prone to confounding due to unrecorded covariate information for women seeking care mostly through emergency room settings.

HEG may be associated with modest increases in risk of preterm birth and low birth weight,[33] however recent studies have suggested these associations can be attributed to maternal characteristics.[34,35]

TABLE 3 Analysis of mean birth weight difference among pregnant women with term live births seen at UNC Health Care between 2014 and 2017 with ondansetron or comparator antiemetic exposure

			Crude		IPT-weighted		Additional adjustment for gestational age	
Full population	N	Mean birth weight, grams (SD)	Difference in means (g)	95% CI	Difference in means (g)	95% CI	Difference in means (g)	95% CI
Ondansetron	1117	3354 (480)	40	−11.9, 91.9	6.9	−48.7, 62.4	8	−44.0, 60
Comparators	541	3314 (451)	0		0		0	
Per-protocol								
Ondansetron	934	3354 (481)	40.2	−12.1, 92.6	3.8	−51.2, 58.8	4.6	−47.2, 56.3
Comparators	423	3314 (449)	0		0		0	
Administered								
Ondansetron	399	3295 (471)	−10.1	−89.3, 69.1	−52.3	−141.6, 37.1	−78.4	−165.7, 8.9
Comparators	243	3305 (451)	0		0		0	
Prenatal care								
Ondansetron	779	3373 (490)	77.5	7.8, 147.3	9	−67.6, 85.6	17.3	−55.2, 89.7
Comparators	303	3296 (454)	0		0		0	

Abbreviations: CI, confidence interval; g, grams; UNC, University of North Carolina.

Similar proportions of women in each antiemetic group in our analysis had hospitalizations or emergency room visits for HEG, therefore any effect of HEG on the study outcomes is unlikely to be a source of confounding. No published studies have used an active comparator of alternative antiemetic users to estimate the risk of late pregnancy outcomes. A study of all pregnancies in Denmark reported no association between ondansetron use and preterm birth or birth weight compared to non-users of ondansetron.[9] Ondansetron exposed births in western Australia had higher risk of preterm birth, preeclampsia, and low birth weight compared to non-users[8]; analyses for preeclampsia and low birth weight did not control for confounding, therefore inference from this analysis is limited. Unlike the current study, ondansetron use was very rare (<1% of all pregnancies) in both of these studies and hospitalizations for HEG were common (35-56%) among women using ondansetron.[8,9]

We analyzed women starting at the gestational age of their first eligible antiemetic prescription and accounted for all events subsequent to that prescription. Alternatively, some analyses of late pregnancy outcomes condition on survival until live birth or the start at-risk period, which is the start of the 21st week of pregnancy. Each of these analyses answer different questions: (a) what is the comparative risk of the outcome at the time of exposure, given that a woman may experience events that result in her not being at-risk for the outcome? And (b) what is the comparative risk of the outcome if a woman is still pregnant and now at risk for the outcome, and previously took an antiemetic? In the current study, the risk of miscarriage and termination events occurring before the start of the 21st week of pregnancy did not differ between antiemetic exposure groups, therefore results were very similar between the main and conditional analyses. Which question is most important for regulatory or clinical decision making, and whether results from conditional analyses could be considered biased, is the source of continued debate and discussion.[36,37]

The small number of cases limits our results for stillbirth. Only three cases were observed in the comparator group. Similarly, the small sample size in sensitivity analyses prevented us from making strong conclusions. Advantages of using EHR data for studying pregnancy include the availability of gestational age and delivery data, including birth weight. While larger sample sizes and data on prescription fills can be attained in insurance claims databases, the inability to accurately assign gestational age can be problematic for studying gestational-age specific exposures and outcomes, such as preterm birth and non-live birth outcomes.[38] Hypertensive disorders were defined using diagnosis codes only and were not subject to chart review. We restricted to inpatient diagnoses to decrease the number of false cases captured, as was demonstrated in validation studies of claims databases.[17,18] The incidence of gestational hypertensive disorders was higher than expected in our sample, which likely reflects both the higher proportion of high-risk pregnancies seen in the maternal and fetal care department at UNC Hospital, and some inclusion of non-cases.

Our study was designed to answer whether ondansetron is as safe as other commonly recommended and used antiemetics to treat nausea and vomiting among women who are seeking pharmacological treatment. We cannot comment on whether ondansetron or the comparator drugs increase the risk of adverse outcomes compared to no pharmacological treatment. For women in need of symptom relief, the comparator question is relevant and informative because it addresses the clinical question faced by the physician and patient. Previous research has been mixed on the safety of comparator drugs for these outcomes, but well-designed studies suggest no increase in risk associated with promethazine or metoclopramide use.[39-45]

In summary, we did not observe evidence of a difference in risk of preterm birth and gestational hypertensive disorders between ondansetron users and comparator antiemetic users. We did observe

a potential increase in risk of having an SGA infant; these results warrant further investigation. Our findings, based on a rigorous active comparator analysis that reduced confounding by design, adds to the body of literature assessing the safety of ondansetron use during pregnancy.

ETHICS STATEMENT

This study was approved by the UNC Institutional Review Board.

CONFLICT OF INTERESTS

Drs. Jonsson Funk and Stürmer receive salary support from the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences Inc, Merck, and Shire). Dr Stürmer is a stockholder in Novartis, Roche, BASF, AstraZeneca, Johnson and Johnson, and Novo Nordisk. Dr. Jonsson Funk is a scientific steering committee member for GlaxoSmithKline and receives a consulting fee. Dr. Lund's spouse is a full-time, paid employee of GlaxoSmithKline and holds > $40 000 in stock in the company. Drs. Suarez, Boggess, and Engel have no conflicts to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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