USE OF ONDANSETRON FOR NAUSEA AND VOMITING DURING PREGNANCY AND ADVERSE PREGNANCY OUTCOMES

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ABSTRACT

Elizabeth A. Suarez: Use of ondansetron for nausea and vomiting during pregnancy and the adverse pregnancy outcomes
(Under direction of Michele Jonsson Funk)

Ondansetron, a 5-HT_3-receptor antagonist, is commonly used off-label in the United States to treat nausea and vomiting in pregnancy. Previous studies of adverse pregnancy outcomes offer an incomplete picture of the safety of ondansetron because they use methods that increase the potential for unmeasured confounding or fail to appropriately account for events occurring along the gestational age time scale.

The objective of this project was to compare the risk of various adverse pregnancy outcomes between women exposed to ondansetron during the first 20 weeks pregnancy and women exposed to alternative antiemetic medications, including promethazine and metoclopramide. Adverse outcomes included miscarriage, stillbirth, preterm birth, gestational hypertensive disorders, small for gestational age, and mean birth weight.

A pregnancy cohort was created using electronic health record data from the UNC Health Care system in North Carolina. Women were classified as exposed to either ondansetron or comparator antiemetics (metoclopramide or promethazine) based on the first prescription received in the first 20 weeks of gestation. The cumulative incidence of each outcome was estimated using methods that account for the gestational age of antiemetic exposure and competing events in pregnancy, and risk ratios (RR) and risk differences (RD) were calculated. Measured confounding by was controlled using stabilized inverse probability of treatment weights.

We identified 2677 eligible pregnancies with antiemetic orders, 66% of which first received ondansetron. After adjustment for measured covariates, there was no difference in risk of miscarriage (RR 1.23, 95% CI 0.23, 8.51; RD 2.3%, 95% CI -25.4, 24.1). No association was observed between ondansetron and stillbirth (odds ratio=1.32; 95% CI 0.39, 4.53), preterm birth (RR=0.91; 95% CI 0.40, 2.54), or gestational hypertensive disorders (RR=0.90; 95% CI 0.47, 1.89). Similarly, no association was observed for small for gestational age (RR=1.19; 95% CI 0.52, 3.38) and there were no clinically important differences in mean birth weight among term births. Results from sensitivity analyses were imprecise but did not change conclusions. These results do not offer evidence that ondansetron increases risks of adverse pregnancy outcomes compared to alternative and commonly used antiemetic therapies.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
BMI	Body mass index
CDW	Carolina Data Warehouse
CI	Confidence interval
EDD	Estimated date of delivery
EHR	Electronic health record
FDA	Food and Drug Administration
GHTN	Gestational hypertensive disorders
HEG	Hyperemesis gravidarum
HELLP	Hemolysis, elevated liver enzymes, low platelet count
ICD-9	International Classification of Diseases, 9th Edition
ICD-10	International Classification of Diseases, 10th Edition
IPT	Inverse probability of treatment
IQR	Interquartile range
LMP	Last menstrual period
MICE	Multiple imputation by chained equations
NC TraCS	North Carolina Translational and Clinical Sciences Institute
NSAID	Non-steroidal anti-inflammatory drugs
NVP	Nausea and vomiting of pregnancy
OR	Odds ratio
OTC	Over the counter
PPI	Proton pump inhibitors
PTB	Preterm birth
RD	Risk difference

RR	Risk ratio
SD	Standard deviation
SGA	Small for gestational age
UNC	University of North Carolina

CHAPTER 1: STATEMENT OF SPECIFIC AIMS

Nausea and vomiting are common symptoms experienced by nearly 80% of women during early pregnancy (1). While mild to moderate symptoms may be signs of a healthy pregnancy, frequent symptoms quickly degrade quality of life for the mother, leading to an inability to preform daily functions, loss of employment, and depression (2). Severe vomiting, or hyperemesis gravidarum (HEG), may be associated with low birth weight, preterm birth, and adverse maternal outcomes (2).

The American College of Obstetrics and Gynecology recommends dietary changes and avoidance of triggers as the first approach for mild symptoms (1). Vitamin B6 (pyridoxine) is recommended if diet and lifestyle changes are not effective and is available over-the-counter (OTC). The extended release combination drug doxylamine/pyridoxine, recently made available in the US, is the only FDA approved prescription treatment for nausea and vomiting in pregnancy (NVP) and is recommended as first-line pharmacotherapy. Other pharmacotherapy options include other antihistamines (doxylamine, dimenhydrinate, and meclizine), dopamine antagonists (promethazine and metoclopramide), and lastly for moderate and severe cases, serotonin antagonists (ondansetron). An analysis of US private insurance data suggests at least 20% of women were filling prescriptions for ondansetron at some point during pregnancy in 2014 (3). This high proportion suggests ondansetron is being utilized as a therapeutic option for mild cases of NVP or as a first-line therapy, contrary to guidelines.

The safety of ondansetron during pregnancy is uncertain. The highest quality studies have been completed using national records in Denmark and Sweden, where use of ondansetron is uncommon (<1% of all pregnant women) and limited to women with severe

symptoms and high likelihood of hospitalization (4,5). Large studies in the US have estimated effects on birth defects using insurance claims data and large case-control studies, but have not reported on other types of adverse pregnancy outcomes (6–8). Previous studies of preterm birth with ondansetron use reported no association, but are limited by inadequate control for NVP severity and small sample sizes (5,9,10). Mild/moderate NVP may be associated with a decreased risk of preterm birth and lack of proper adjustment may obscure any true increased risk due to medication use (11–13). One study has reported an increased risk of hypertension/preeclampsia among ondansetron users, but failed to account for NVP as an early symptom of preeclampsia (10). No other studies have investigated the possible increased risk of hypertension/preeclampsia with ondansetron use. Any possible association of ondansetron with miscarriage is confounded by the protective effect of NVP (5,9,14); no previous studies have properly controlled for this important source of confounding. The few studies examining stillbirth risk have been limited to very small numbers of exposed cases, limiting the ability to make strong conclusions (5,9,14).

This study compares the risks of miscarriage, stillbirth, preterm birth, gestational hypertensive disorders, and birth weight between ondansetron users and users of other antiemetic prescription medications. The study population consists of pregnant women seeking care at UNC Health Care clinics and hospitals and will utilizes data from electronic health records (EHR). Prospective definition of exposures and outcomes from time of medication fill allowed for consideration of competing risks.

1.1 Aim 1

The objective of Aim 1 is to assess the safety of ondansetron for treatment of pregnancy-induced nausea and vomiting for the outcome of miscarriage. Women with prescriptions for ondansetron are compared to women with prescriptions for promethazine or metoclopramide. A new user, active comparator design is used to minimize confounding by nausea and vomiting symptoms. Cumulative incidence of miscarriage is estimated using

methods that appropriately account for variable gestational ages at the start of antiemetic use and competing risks due to events that result in women no longer being at risk for miscarriage. Sensitivity analyses minimize the impact of exposure misclassification by censoring at the gestational age of switching antiemetic groups (per-protocol analysis) and limiting antiemetic exposure groups to women who were administered an antiemetic in a healthcare setting to ensure compliance. Additional sensitivity analyses consider a latency period for miscarriage.

1.2 Aim 2

The objective of Aim 2 is to assess the safety of ondansetron for treatment of pregnancy-induced nausea and vomiting for the outcomes of stillbirth, preterm birth, gestational hypertensive disorders, and birth weight. Women with prescriptions for ondansetron are compared to women with prescriptions for promethazine or metoclopramide. A new user, active comparator design is used to minimize confounding by nausea and vomiting symptoms. At-risk periods are carefully designed for each outcome and cumulative incidence is estimated accounting for competing events using appropriate estimators. Unconditional and conditional estimates are compared by considering the entire pregnancy timeline or conditioning on survival until the risk period for the outcomes of interest at the start of the 21st week of pregnancy. Sensitivity analyses minimize the impact of exposure misclassification by censoring at the gestational age of switching antiemetic groups (per-protocol analysis) and limiting antiemetic exposure groups to women who were administered an antiemetic in a healthcare setting to ensure compliance. Sensitivity analyses that restrict to women who received prenatal care at UNC in the first 20 weeks of pregnancy assess the impact of missing covariate data and are generalizable to a population of women who receive regular prenatal care.

CHAPTER 2: REVIEW OF LITERATURE

2.1 Nausea and vomiting in pregnancy

Nausea and vomiting of pregnancy (NVP) is experienced by nearly 80% of women during early pregnancy (1). Symptoms are more common among younger women, multiparous women, and women with multiple gestation pregnancies (12,15–17). Symptoms start in the first trimester for the majority of affected women (15,17,18), and last for about 8 weeks (19). Women seek symptom relief so they can continue daily activities such as work, school, and childcare (20). A small proportion of women, 2-3%, will experience hyperemesis gravidarum (HEG), severe nausea and vomiting during pregnancy that often results in dehydration and hospitalizations (2).

Data from the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial provides a detailed look at nausea and vomiting by gestational week based on data from daily and weekly diaries (18). More than 50% of women reported nausea and nearly 70% reported nausea and/or vomiting by gestational week 5. Nausea symptoms peaked between weeks 9 and 12 when 90% of women reported symptoms at least once per week; approximately 55% of women reported vomiting at least once per week in the same period. Less than 1% of the study population was hospitalized for vomiting or HEG. Age was the only characteristic clearly associated with NVP; younger women were more likely to report symptoms.

The exact causes of NVP are unclear. NVP was thought to be associated with pre-pregnancy weight, race, and sex of the infant, but results from multiple studies are conflicting on these factors (12,15–17). The role of smoking is unclear; some studies reporting an inverse association with NVP while others report no association (15,17,21). The hormone human

chorionic gonadotropin (hCG) may be associated with NVP; peak hCG and peak NVP symptom severity have both been shown to fall between 12 and 14 weeks of gestation (2).

Mild to moderate symptoms have long been believed to be signs of a healthy pregnancy. Results from a secondary analysis of the EAGeR trial support this notion by indicating a strong protective effect of nausea (HR: 0.44; 95% CI: 0.26, 0.74) and nausea with vomiting (HR: 0.20; 95% CI: 0.09-0.44) against clinical pregnancy loss among women with one or two prior losses (18). Other studies of NVP and miscarriage have reported similar inverse associations (19,22). The effect of NVP on other pregnancy outcomes is less certain. An analysis of the Norwegian Mother and Child Cohort Study (MoBa) database reported that women with NVP were more likely to have term births and less likely to have an emergency cesarean section, low birth weight, and a small for gestational age infant than women who were symptom free (13). Women with both nausea and vomiting were more likely to report pelvic girdle pain, high blood pressure before and during pregnancy, proteinuria, and preeclampsia than women who reported no symptoms, while women with nausea alone did not report more hypertensive disorders than symptom free women. This suggests possible differences in pregnancy outcomes by NVP symptom severity. A study from the Swedish Medical Birth Register also reported increased risk of preeclampsia with severe symptoms, specifically with HEG in the second trimester (23). HEG may be associated with low birth weight and preterm birth, but little evidence exists for other outcomes (24,25).

One study estimated the economic burden of NVP in the US to be $1.8 billion in 2012, with an average cost of therapy equaling $1827 per treated woman (26). This estimate includes direct costs of medications and healthcare utilization and indirect costs of time off work and loss of productivity. NVP represents a significant burden on society, and more evidence on the safety of commonly used treatments can bolster or reshape guidelines for the benefit of a large population of pregnant women.

2.2 Treatment for nausea and vomiting in pregnancy

The American College of Obstetrics and Gynecology (ACOG) recommends dietary changes and avoidance of triggers as the first approach for mild symptoms (27). First line options for pharmacotherapy include pyridoxine (vitamin B6) or doxylamine/pyridoxine (Unisom/vitamin B6) based on evidence of safety and effectiveness over placebo. Doxylamine/pyridoxine was approved under the brand name Diclegis in the US in 2013, and currently is the only FDA approved therapy for NVP. Doxylamine/pyridoxine is not indicated for HEG and cannot be administered intravenously. If ineffective, the ACOG recommends other antihistamines (dimenhydrinate [Dramamine], and meclizine [Bonine]) and dopamine antagonists (promethazine [Phenergen]). For persistent symptoms, metoclopramide (Reglan), serotonin antagonists (ondansetron [Zofran]), and trimethobenzamide (Tigan) are recommended.

Trends in antiemetic prescribing in the US were assessed using the Sentinel Distribution Database, which includes data from private insurance plans from across the US (3). Among women with live births in 2014, 22% filled a prescription for ondansetron at some point during pregnancy. Use of ondansetron increased dramatically from the beginning of the study period in 2001 when less than 1% of live birth pregnancies filled prescriptions. In the same period, the proportion of live birth pregnancies filling promethazine prescriptions decreased from 14% to 8% and the proportion of live birth pregnancies filling metoclopramide was unchanged at approximately 3%. Trends in antiemetic prescription fills changed in 2007 when promethazine and metoclopramide use peaked and ondansetron use started to increase steadily. This is consistent with timing of the first generic approvals of ondansetron in 2007.

A review published in JAMA summarized evidence of effectiveness of antiemetic therapies from randomized clinical trials and observational studies (28). All pharmacologic options appeared more effective than placebo at symptom control for their recommended symptom severities. Head-to-head trials suggest ondansetron is more effective than

doxylamine/pyridoxine but offers similar symptom control as metoclopramide. Only ondansetron had evidence of effectiveness at all symptom levels. Notably, ondansetron users reported fewer side effects than metoclopramide users (29). Metoclopramide, promethazine, doxylamine/pyridoxine, and other antihistamines all share a common side effect of drowsiness. The effectiveness of ondansetron across all severities combined with the more tolerable side effect profile has likely contributed to the recent increase in prescribing since generic versions first became available.

The FDA first issued a warning that ondansetron use may be associated with abnormal heart rhythms (QT prolongation) in September 2011 (30). In December 2012, the 32 mg single intravenous dose was removed from the market due to updated data on the risk of QT prolongation (31). Serotonin 5-HT_3 receptor antagonists can lead to serotonin syndrome, a condition that results in high levels of circulating serotonin due to use of multiple serotonin-modifying drugs. The ACOG notes the following medications to be contraindicated for use with ondansetron, some for their serotonin-modifying effects: antihistamines, analgesics and sedatives, diuretics, anticholinergics, antiarrhythmics, antipsychotics, tricyclic and tetracyclic antidepressants, macrolide antibiotics, trazodone, fluoxetine, antimalarials, metronidazole, and human immunodeficiency virus protease inhibitors (1). This list includes commonly used selective serotonin reuptake inhibitors that are used by approximately 6% of women at some point during pregnancy in the US (32). Interactions between drugs should be considered before prescribing ondansetron (33).

2.3 Safety of antiemetics in pregnancy

2.3.1 Published studies on the safety of ondansetron during pregnancy

Multiple studies have been published that investigate various pregnancy outcomes after use of ondansetron and other antiemetics. Most of these studies have only evaluated the risk of birth defects or have been completed outside of the US where large cohorts or national health systems provide large populations and detailed medication data. Differences in drug approvals

and prescribing preferences in other countries limits the generalizability of results to the US. In Canada, the Motherisk program, a teratology research group based in Toronto, has focused heavily on the safety and effectiveness of the combination drug doxylamine/pyridoxine due to its high uptake there (34). Large studies concerning ondansetron have been completed in Denmark and Sweden where less than 1% of all pregnant women used ondansetron during the time of study (4,5,35). In 2018, three studies were published using large US populations, but focused exclusively on birth defects (6–8); two of these studies included very large populations of ondansetron users from Medicaid and private insurance claims (6,8). Other studies completed in the US have used highly selected populations, only include women with HEG, or focused only on birth defects (14,36,37). A brief overview of all observational safety studies for ondansetron is summarized in Table 2.1.

Five observational safety studies have focused on outcomes other than birth defects (5,9,10,14,38). The most recent and sizable of these studies was conducted using the Danish Medical Birth Register (5). The authors assembled a cohort including 1,970 ondansetron users from 2004 through 2011 from eligible pregnancies nationwide, corresponding to a use prevalence of 0.3%. They reported no increase in risk among ondansetron users for spontaneous abortion, stillbirth, major defects, preterm birth, low birth weight, or small for gestational age infants, compared to non-users. An active comparator sensitivity analyses compared ondansetron users to antihistamine users for analyzing spontaneous abortion and accounted for much but not all of the protective effect of NVP. Given the possible protective effect of NVP on other pregnancy outcomes (18), use of this active comparator for other outcome analyses would be informative.

A recent study in the US included women recruited online with a history of HEG (14). Eligibility criteria included treatment with intravenous fluids, parenteral nutrition, or a feeding tube in at least one pregnancy. Recruited women then invited acquaintances with at least two pregnancies surviving past 27 weeks that were unaffected by NVP to serve as an unexposed

group. Women with HEG history were classified as exposed or unexposed to ondansetron by pregnancy; this resulted in 772 women with history of HEG contributing 1070 pregnancies to the ondansetron exposed group and 771 pregnancies to the ondansetron unexposed group. Comparisons were made between the HEG/ondansetron group and the HEG/no ondansetron group or the no HEG group. The authors concluded that there was no difference in preterm birth between ondansetron users and non-users among women with a history of HEG after an unadjusted comparison of the proportion of live births that ended in preterm birth. However, once accounting for non-live births by using all pregnancies as the denominator, the ondansetron users had twice the proportion of preterm birth. Nevertheless, these analyses did not account for confounding or correlation between pregnancies among the same woman. Comparisons with the symptom-free group were biased by the enrollment criteria of requiring women to have had two pregnancies that survived past 27 weeks, ensuring this comparison group had a lower risk of spontaneous abortion, termination, and preterm birth than the HEG/ondansetron exposed group. Overall, this study provides weak evidence of the safety of ondansetron use due to multiple methodological flaws and the exclusion of women with NVP that does not progress to HEG (39).

Other studies of non-defect outcomes relied on very small samples of ondansetron-exposed women. A population based study of all live births and stillbirths in Western Australia reported on 291 ondansetron exposed births, corresponding to approximately 0.3% of births (10). Compared to non-users, ondansetron users had an overall increase in risk of pregnancy complications. Analyses of specific complications were inconclusive due to small numbers of exposed cases ($n<35$), and the authors concluded that while no adverse outcomes were detected, results are inconclusive. A report from the Motherisk program, which established hotlines in North America to counsel women on teratogens and NVP treatments, concluded no increase in risk of miscarriage, stillbirth, termination, major defects, birth weight, or gestational age at birth among women using ondansetron compared to women using other antiemetic or

other non-teratogenic medications (9). However, the sample size was small (176 ondansetron users) and analyses were unadjusted for potential confounders. This sample is also unlikely to be generalizable as it only included women who voluntarily called a hotline to learn more information about a drug they were prescribed. Finally, a small cohort from women referred to the Emery Women's Mental Health Program in early pregnancy were followed until a week after delivery for outcomes (40). Results indicated a possible increase preterm birth and decrease in birth weight among women exposed to ondansetron or promethazine compared to women exposed to neither, but analyses were not adjusted for potential confounders. No differences were reported for neurobehavioral outcomes. The small sample (143 exposed), combined exposure group of ondansetron or promethazine users, and unadjusted comparison to non-users in a selected population of women referred to a mental health facility result in this study offering only weak evidence of the safety of ondansetron.

The remaining studies listed in Table 2.1 have focused on birth defects as the outcome of interest. Evidence of the risk of specific major defects has been mixed. Early results from the National Birth Defects Prevention Study suggest that ondansetron users have increased risk of cleft palate defects compared to non-users with NVP (OR: 2.37, 95% CI: 1.18, 4.76) (36). Analysis of data from later years of the same study suggest an attenuated and uncertain effect among ondansetron users compared to non-users (OR: 1.5, 95% CI: 0.9, 2.5) (37). This study, published only in abstract form, also suggested a possible increase in risk of hypoplastic left heart syndrome, diaphragmatic hernia, and renal agenesis/dysplasia, although acknowledged that exposed cases were few and estimates were unstable. Studies from the Danish Medical Birth Register reported conflicting results, with one analysis finding an increased risk of heart defects among ondansetron users compared to non-users (35), and the other study reporting no evidence of increased risk of any major defects (4). One study was only published in abstract form (35), therefore not enough information is available to speculate about reasons for the conflicting results. Other, smaller studies have not reported increased risk of defects with

ondansetron use (5,9,10,14). A systematic review concluded there is potential small increase in risk of cardiac defects with ondansetron use and that ondansetron should be utilized as a last-resort option for this reason (41), while an updated review reported no significant increase in risk for any defect subgroup (42). In response to the uncertainty surrounding the risk of cardiac and cleft palate defects, three studies were recently completed and published in the US (6–8). An analysis of Medicaid recipients found a small increase in risk for oral cleft among ondansetron users compared to non-users or compared to alternative antiemetic users, but no association with cardiac defects or major defects overall (8). An analysis of privately insured women reported an increase in risk for cardiac defects and orofacial clefts when compared to ondansetron non-users (6). Finally, data from the National Birth Defects Prevention Study and the Slone Birth Defects Study reported associations between ondansetron and cleft palate and renal agenesisdysgenesis (7). The proposed study will not investigate defects and instead of focus on various maternal and fetal outcomes that are comparatively understudied.

2.3.2 Published studies on the safety of other antiemetics

Evidence about the safety of promethazine is sparse and focused on birth defects (Table 2.2). A case-control study in Hungary reported no association between promethazine use and birth defects, although the majority of promethazine use occurred in the middle of pregnancy and the main indications were threatened abortion and preterm delivery (43). A study of women with attempted suicide with large doses of promethazine also did not show any teratogenic effect when limited to exposures during the critical period for defects (44). Studies of phenothiazines, the class of dopamine antagonists that includes promethazine, have not reported an increased risk of malformations (45). A large study from the Swedish Medical Birth Register compared promethazine users to all pregnancies in the register and reported statistically significant but low odds ratios for preterm birth (OR: 1.12, 95% CI 1,02, 1.24) and low birth weight (OR: 1.21, 95% CI: 1.06, 1.39) (46). The study of promethazine overdoses did

not report any differences in preterm birth or low birth weight, however is based on a comparison of matched unexposed siblings (44).

The safety of metoclopramide has been the subject of a few large studies, most recently in a study of the Danish Medical Birth Register that used nearly identical methods to the study of ondansetron (47) (Table 2.3). This study reported no increased risk of spontaneous abortion, stillbirth, major defects, preterm birth, low birth weight, and fetal growth restriction among metoclopramide users compared to non-users with hazards ratios and odds ratios very close to 1. A protective effect for miscarriage was reported compared to non-users (HR: 0.35, 95% CI: 0.33, 0.38); this protective effect was attenuated but still strong when compared to a group of antihistamine users (HR: 0.57, 95% CI: 0.44, 0.73). A large study from Israel reported a possible small increase in risk of preterm birth (OR: 1.15, 95% CI: 0.99, 1.34) and very low birth weight (OR: 1.18, 95% CI: 0.90, 1.54) compared to non-users (48). Data from a teratogen information line suggested a large increase in risk of preterm birth among metoclopramide users compared to non-users, however the sample size was small (n=175 metoclopramide users) and risk ratio estimates were unadjusted (49). Alternatively, a study of women in the Swedish Medical Birth Register reported decreased risk of preterm birth and low birth weight (46). Other studies have reported no increased risk of birth defects among metoclopramide users compared to non-users (36,50).

2.3.3 Limitations of available research on ondansetron

A key limitation of the current body of research for non-defect outcomes is that included ondansetron users are not representative of the current average ondansetron user in the US. This is partly due to the sharp increase in ondansetron use in the US over the past 8-10 years; older studies could not have captured this population. Therefore, current knowledge generalizes only to a selected population of women with severe NVP symptoms and HEG. Current evidence suggests that approximately 20% of pregnant women were filling prescriptions for ondansetron at some point in pregnancy in the US in 2014 (3); these women have milder symptoms that

previously would have remained untreated or have been treated with one of the ACOG recommended therapies. Studies from outside the US, including Denmark and Australia, similarly present results for populations of women with severe NVP symptoms or HEG (5,10). Less than 1% of pregnant women in both populations were exposed to ondansetron, and 30-50% of ondansetron users were hospitalized for HEG at least once during pregnancy.

The small number of exposed cases also limits the ability of previous studies to make definitive conclusions. The Danish Medical Birth Register study only included 32 exposed spontaneous abortions and 6 exposed stillbirths (5). The Australian report included 34 exposed preterm births and 17 exposed preeclampsia cases (10).

Additionally, all studies used ondansetron non-users as the main comparison group. The recent sharp increase in ondansetron dispensing in the US was not met with a sharp decline in other therapies (3). Instead, it appears that more women with NVP symptoms are being treated with pharmacologic options than previously, and ondansetron is a new drug of choice. Studies that compare ondansetron users to non-users do not answer the most clinically relevant question: does ondansetron increase risk to the mother and fetus more than other common pharmacologic options? Non-user comparisons are also prone to confounding and inclusion of immortal time in the analysis. Direct comparison to users of other antiemetics offers methodological advantages over previous study designs.

Table 2.1: Summary of published studies of safety of ondansetron use in pregnancy

Reference	Sample	Comparison	Outcomes	Conclusions
Einarson, 2004 (9) *Canada*	Motherisk (women calling help line)	Ondansetron users (n=176) *vs* other antiemetic users (n=176) *and* various non-teratogenic drug users (n=176)	Live birth, miscarriage, stillbirth, abortion, major defects, birth weight, gestational age at birth	No evidence of increased risk for ondansetron users
Anderka, 2012 (36) *US*	National Birth Defects Prevention Study	Ondansetron users (n=55) *vs* non-users with NVP (n=4020)	Cleft lip/palate, cleft palate, neural tube defects, hypospadias	Increased risk of cleft palate among ondansetron users
Colvin, 2013 (10) *Australia*	Linked state health administrative data	Ondansetron users (n=261) *vs* non-users (n=96,447)	Maternal and child characteristics, birth defects, pregnancy, and delivery characteristics	Possible increase in risk of pregnancy complications among ondansetron users
Pasternak, 2013 (5) *Denmark*	Danish Medical Birth Register	Ondansetron users (n=1970) *vs* non-users (n=~7000)	Miscarriage, stillbirth, major defects, preterm birth, low birth weight, small for gestational age	No evidence of increased risk for ondansetron users
Andersen, 2013 (abstract only) (35) *Denmark*	Danish Medical Birth Register	Ondansetron users (n=1248) *vs* non-users (n=895,770)	Major defects	Twice the prevalence of heart defects among ondansetron users
Danielsson, 2014 (4) *Sweden*	Swedish Medical Birth Register	Ondansetron users (n=1349) *vs* non-users (n=1,500,085)	Any major defect, severe defects, cardiovascular defects, septum defects	Increase in prevalence of septum defects, cardiovascular defects among ondansetron users
Larrimer, 2014 (40) *US*	Emory Women's Mental Health Program	Ondansetron or promethazine users (n=143) vs antiemetic non-users (n=407)	Neurobehavioral and obstetric outcomes	No evidence of increased risk for ondansetron/ promethazine users
Van Bennekom, 2015 (abstract) (37) *US*	Slone Birth Defects Study, National Birth Defects Prevention Study	Ondansetron users vs non-users (N not reported)	Major defects	Possible increase in risk for specific defects among ondansetron users, but estimates unstable
Fejzo, 2016 (14) *US*	History of HEG with intravenous fluids or parenteral nutrition/feeding tube	Ondansetron users with HEG (n=1070) *vs* non-users with HEG (n=771) *and* non-users with NVP (n=1555)	Termination, miscarriage, stillbirth, preterm birth, birth defects	Decreased reports of miscarriage and termination among ondansetron users
Parker, 2018 (7) *US*	Women with NVP from the Slone Birth Defects Study, National Birth Defects Prevention Study	Ondansetron users (n=628) *vs* untreated NVP (n=11,457) *and* alternative antiemetic users (n=539)	Major defects	Possible increase in risk for cleft palate and renal agenesis-dysgenesis in ondansetron users

Reference	Sample	Comparison	Outcomes	Conclusions
Huybrechts, 2019 (8) *US*	Medicaid recipients	Ondansetron users (n=88,467) *vs* non-users (n=1,727,947) *and* alternative antiemetic users (n=185,876)	Cardiac malformations, oral clefts, and major defects	Increase in risk for oral clefts in ondansetron users
Zambelli-Weiner, 2019 (6) *US*	Privately insured women (Truven Health Analytics)	Ondansetron users (n=76,330) *vs* non-users (n=787,753)	Cardiac defects, orofacial clefts	Increase in risk for cardiac defects and orofacial clefts in ondansetron users

Table 2.2: Summary of published studies of safety of promethazine use in pregnancy

Reference	Sample	Comparison	Outcomes	Results
Asker, 2005 (46) *Sweden*	Swedish Medical Birth Registry	Promethazine users (n=1961) *vs* all pregnancies (n=665,672)	Preterm birth, low birth weight, small for gestational age, major malformations	Possible increased risk of preterm birth and low birth weight among promethazine users
Bartfai, 2008 (43) *Hungary*	Hungarian Congenital Abnormality Registry	Promethazine users (n=9673) *vs* non-users (n=51,321)	Major defects	No evidence of increased risk among promethazine users
Petik, 2008 (44) *Hungary*	Self-poisoned pregnant women and Hungarian Case-Control Surveillance of Congenital Abnormalities	Promethazine overdosers (N=32) *vs* sibling pregnancies without promethazine exposure (N=32)	Defects, low birth weight, preterm birth, cognitive and behavioral status	No evidence of increased risk among promethazine overdoses
Gilboa, 2009 (51) *US*	National Birth Defects Prevention Study	Promethazine users (n=127) *vs* non-users of any antihistamine (n=4445)	Specific major defects	Increased risk of neural tube defects, spina bifida, ventricular septal defects among promethazine users
Anderka, 2012 (36) *US*	National Birth Defects Prevention Study	Promethazine users (n=200) *vs* non-users with NVP (n=4020)	Cleft lip/palate, cleft palate, neural tube defects, hypospadias	Possible increased risk of neural tube defects among promethazine users

Table 2.3: Summary of published studies of safety of metoclopramide use in pregnancy

Reference	Sample	Comparison	Outcomes	Results
Sorensen, 2000 (50) *Denmark*	Danish Medical Birth Registry	Metoclopramide users (n=309) *vs* non-users of any drugs (n=13,327)	Birth defects, low birth weight, preterm delivery	No evidence of increased risk among metoclopramide users
Berkovitch, 2000 (52) *International*	Women calling teratogen information call lines	Metoclopramide users (n=126) *vs* various non-teratogenic medication users (n=126)	Major defects, miscarriage, abortion, fetal death, gestational age at delivery, birth weight, fetal distress	No evidence of increased risk among metoclopramide users
Berkovitch, 2002 (49) *International*	Women calling teratogen information call lines	Metoclopramide users (n=175) *vs* various non-teratogenic medication users (n=175)	Major defects, miscarriage, abortion, fetal death, gestational age at delivery, birth weight, fetal distress	Three times the risk of preterm birth among metoclopramide users
Asker, 2005 (46) *Sweden*	Swedish Medical Birth Registry	Metoclopramide users (n=1166) *vs* all pregnancies (n=665,672)	Preterm birth, low birth weight, small for gestational age, major malformations	Possible decrease in risk of low birth weight and small for gestational age infants among metoclopramide users
Matok, 2009 (48) *Israel*	Clalit Health Services database	Metoclopramide users (n=3458) *vs* non-users (n=78,245)	Major defects, low birth weight, preterm delivery, perinatal death	No evidence of increased risk among metoclopramide users
Anderka, 2012 (36) *US*	National Birth Defects Prevention Study	Metoclopramide users (n=23) *vs* non-users with NVP (n=4020)	Cleft lip/palate, cleft palate, neural tube defects, hypospadias	Possible increased risk of cleft palate among metoclopramide users
Pasternak, 2013 (47) *Denmark*	Danish Medical Birth Register	Metoclopramide users (n=45,002) *vs* non-users (n=~150,000)	Miscarriage, stillbirth, major defects, preterm birth, low birth weight, small for gestational age	No evidence of increased risk for metoclopramide users

CHAPTER 3: METHODOLOGICAL CONSIDERATIONS OF THE RESEARCH QUESTION

Analyzing pregnancy outcomes introduces a series of challenging design and analysis issues. Failure to consider the gestational age of entry into the analysis and competing events can result in substantial bias in pregnancy studies (53). This complexity is often overlooked in perinatal pharmacoepidemiology because many study populations are limited to women with live births due to limitations of administrative data sources. However, with the appropriate data, survival analysis methods can be used to appropriately account for late entry and competing events by correctly assigning time at risk (53).

3.1 New user active comparator design

The proposed study will use a new user, active comparator design by comparing ondansetron use to the combined comparator group of promethazine or metoclopramide use. Ondansetron, promethazine, and metoclopramide are all indicated for treatment of moderate NVP and have evidence of similar effectiveness (28). All three therapies are recommended after treatment with doxylamine/pyridoxine is unsuccessful, therefore first use of any of these prescriptions may represent use after OTC remedies have failed. Comparing ondansetron to promethazine or metoclopramide addresses a clinically important question: is ondansetron safe compared to recommended alternative therapies?

The new user design identifies members of a population at the point of study drug initiation to identify a clear time zero for the start of follow-up (54). Use of active comparator minimizes confounding and asks a clinically relevant question about which of two treatment choices is the most effective or safe (55). There are few examples of new user, active comparator designs in studies of perinatal medication use. Few medications are initiated during

pregnancy and studies instead aim to assess the safety of continued use of medications for chronic conditions that existed prior to the start of pregnancy. Limited literature on safety leads to channeling patients to treatments that are widely considered to be safe, limiting the ability to conduct active comparator studies. The proposed study aims to investigate medications that are initiated for treatment of a pregnancy related symptom, therefore the study question fits naturally with a new user, active comparator design.

This design also simplifies issues common to perinatal epidemiology by establishing a clear start time for follow-up. These issues include left truncation, which results from entry into the cohort after theoretical time zero, or starting follow-up after the cohort defining event has occurred (56). In studies of miscarriage, left truncation is common because women enter the study cohort later than conception and miscarriage may occur as early as conception. Left truncation results in selection bias when survival time is less than the truncated time, such as when a miscarriage occurs before the woman is able to be recruited into the study cohort (56). New user, active comparator designs minimize the potential for selection bias due to left truncation by design. All subjects are entered into the cohort at the beginning of either the exposure of interest or the active comparator which creates an observable time zero for all subjects (54).

Variable exposure start times can still have an impact on risk estimation in an active comparator study due to changes in risk of pregnancy outcomes as weeks of gestation progress. For example, the risk of miscarriage is greater at early gestational ages than later gestational ages within the first 20 weeks of pregnancy (57). If treatment A is more likely to be initiated at an earlier gestational age than treatment B, we will observe more miscarriages among women exposed to treatment A due to the higher risk of miscarriage at earlier gestational ages and observation of a longer risk period. This will artificially inflate the risk of miscarriage among women exposed to treatment A compared to women exposed to treatment B. This may also impact the analysis of pregnancy outcomes that occur after 20 weeks of

gestation because miscarriages are competing events, therefore creating differential competing risks between exposure groups. The new user design is expected to decrease the differential in antiemetic start times across women receiving prescriptions for different antiemetics because use of the first antiemetic is captured, theoretically at the start of NVP symptoms. If the distribution of gestational ages of first antiemetic use differs between active comparator groups, this difference should be adjusted through matching or other covariate control methods.

The new user active comparator design will also reduce the potential for confounding by comparing exposure groups based on first treatment used. One important source of confounding is severity of NVP. If we were to compare ondansetron use at any time to promethazine use at any time, there may be substantial confounding by indication because the ondansetron users are more likely to have already failed treatment on promethazine or other antiemetics for mild or moderate symptoms. By instead comparing new users of ondansetron to new users of promethazine, excluding use of either antiemetic before the first prescription of the other, we are comparing women initiating their first prescription antiemetic and hopefully reducing the discrepancy in NVP severity and the possibility of confounding by indication. The study period also represents a time when treatment patterns in the US suggest these antiemetics were somewhat interchangeable.

3.2 Competing risks and estimation of unconditional risk

The outcomes considered in Aim 2 occur in the second half of pregnancy after 20 completed weeks of gestation. Women are not considered at risk for the outcomes of stillbirth, preeclampsia, and preterm birth until after the 20th week of gestation because, by definition, none of these events could occur before 20 weeks. This results in the common practice of restricting study populations to pregnancies that survive until 20 weeks regardless of the timing of the exposure. For example, an analysis of the risk of preeclampsia will only include women who remain pregnant at 20 weeks of gestation because preeclampsia cannot be diagnosed before this time. From the perspective of defining the outcome, this approach seems logical

because the outcome will be undefined before 20 weeks of gestation. However, if examining the effect of an exposure that occurs before 20 weeks, this approach neglects events that occur after initiation of the exposure and before the risk period begins. To conceptualize the issues with this approach, it is useful to consider the design of a randomized trial that investigates the effect of an early pregnancy treatment on a late outcome. A trial of antiemetics and the risk of preeclampsia would randomize women at a given gestational week to one of two antiemetic drugs and then follow the women forward for preeclampsia diagnosis or end of pregnancy. If pregnancy ends before 20 weeks in cases of termination or miscarriage, these pregnancies would not be excluded from the study population but rather analyzed through censoring, a competing risks analysis, or as a composite endpoint.

Additionally, pregnancies that reach 20 weeks of gestation are simultaneously at risk for multiple outcomes. For example, a pregnancy that ends in stillbirth at 25 weeks is no longer at risk for the other outcomes of hypertension, preeclampsia, and preterm birth. Similarly, a pregnancy that ends in live birth at week 38 is no longer at risk for stillbirth. When using traditional survival analyses methods, analyzing the outcome of interest as a simple binary does not appropriately handle these competing event types. Traditional survival analysis follows patients from the start of follow-up until the time of event or censoring; censoring assumes the event time is unobserved during the study but will occur at a time later than the censoring time. For an analysis of stillbirth, it would be incorrect to assume the event time (stillbirth time) is unobserved but greater than the time of live birth because an infant born alive is no longer at risk for stillbirth. Therefore, events that result in the pregnancy no longer being at risk for the event of interest should be treated at competing events.

Conditional risk is defined as the risk of an event if all competing risks were removed from the population (58). This is achieved through exclusion of people who experience a competing event from the study population. Conditional risk estimates are valid estimates of risk if the competing events are independent of the outcome of interest, meaning the risk of the

outcome would be the same if no competing risks occurred (58). This assumption is questionable for pregnancy outcomes; it is unlikely that an intervention that eliminates the risk of spontaneous abortion would have no effect on the risk of stillbirth, preeclampsia, or preterm birth.

Unconditional risk is defined as the risk of an event allowing competing risks to occur (58). This involves estimation of the cumulative incidence for each mutually exclusive event. These estimation methods define the risk set for the outcome of interest by including both individuals that are free of any event and individuals who experienced a competing event (59). This strategy effectively constrains the risk estimate and avoids overestimating the risk of the outcome of interest, which occurs when individuals experiencing competing events are censored.

3.2.1 Methods used for estimating cumulative incidence and risk contrasts

Risk ratios and risk differences for study outcomes comparing antiemetic groups were estimated using non-parametric survival analysis methods. Cumulative incidence of the outcome was estimated in each antiemetic group using an estimator that can appropriately account for left truncation due to late entry and multiple event types due to competing events. The Fine and Gray estimator allows for estimation of covariate effects on the cumulative incidence of multiple event types (60). This estimator has been extended to additionally account for left truncation (61,62); in this study, methods that account for left truncation were used to account for receipt of antiemetic prescriptions after gestational day 0. Cumulative incidence estimates were divided or subtracted, using the alternative antiemetic group as the reference, to estimate risk ratios and risk differences, respectively, and empirical 95% confidence intervals were estimated using the 2.5^{th} and 97.5^{th} percentiles of the distribution of 1000 bootstrap samples (63).

Follow-up started at the gestational age of the first eligible antiemetic prescription or two days after the first prescription, depending on the outcome of the analysis. In a small number of

cases, the pregnancy was first identified by early pregnancy code or pregnancy episode start at a gestational age later than the first eligible antiemetic prescription. In these cases, follow-up started at the gestational age of first pregnancy identification rather than at the gestational age of the first eligible antiemetic prescription to avoid incorporating immortal time in the analysis.

3.3 Misclassification of antiemetic exposure status

The duration of antiemetic use in pregnancy is typically short. Prescriptions are written for supplies of 7-30 days, or sometimes less. Women may receive prescriptions for more than one specific antiemetic if symptom control is not achieved or if different drugs are used during the day and at night. Women may receive prescriptions for antiemetics but never take them. These scenarios can result in exposure misclassification. Exposure will be defined based on a first-treatment-carried-forward methodology that assigns exposure as a time-fixed variable based on the first prescription received in pregnancy. While this approach offers analytic simplicity, it may introduce exposure misclassification by misclassifying women who later switch to the comparator treatment. Use of an active comparator means non-differential misclassification of exposure that is likely in a first-treatment-carried-forward design is not expected to be towards the null (64).

An per-protocol approach can be used to take into account women who receive a prescription for a different antiemetic after their first prescription (65). These women will be removed from the analysis through censoring at the gestational age of their second prescription. This will estimate the effect of exposure to only ondansetron or only promethazine or metoclopramide.

Exposure misclassification can also result from lack of use of prescribed antiemetics. Limiting the antiemetic exposure definition to orders administered in a health care setting, either in an inpatient or emergency room setting or by intravenous administration, will restrict the study population to women with a very high likelihood of being exposed to the antiemetic.

3.4 Methods for handling small risk sets when start of follow-up is greater than 0

An issue of importance for Aim 1, which estimates the risk of miscarriage, is how to handle small risk sets that result from entering the analysis at the gestational age of first eligible antiemetic order rather than at gestational age 0. Due to this design, the population at risk of miscarriage grows with gestational age as women are exposed to eligible antiemetics and enter the analysis. Miscarriage events that occur early in gestation when the population at risk is small can artificially inflate the cumulative incidence estimate because the denominator is small (66). To limit the influence of early events, we postponed event times for miscarriage and termination events that occurred when the population at risk was smaller than 50 pregnancies. Event times were changed to the gestational age when the risk set reaches or exceeds 50 pregnancies (66). Postponing event times allows for estimation of cumulative incidence based on all observed miscarriage cases without excluding outcomes or conditioning on survival.

Other methods for handling small risk sets were also considered. Early events can be excluded from the analysis by starting follow-up at a gestational age where the population at risk exceeds a specified minimum (67). This approach conditions on survival of the pregnancy until a specific gestational age. Women with miscarriages (or any event that ends follow-up) prior to the new start of follow-up would not be eligible in the analysis. This approach changes the interpretation of the results by limiting the study population to women with pregnancies that survive until a specified gestational age. If early exposure changes the risk of early pregnancy loss and these outcomes are excluded from the analysis, results may be misleading. A second alternative approach is to ignore events that occur at gestational ages when the risk set is smaller than a specified minimum (68). This method does not exclude the pregnancy from the analysis, but rather reclassifies the pregnancy as not having an early miscarriage. This approach could lead to biased results by misclassifying the outcome. The chosen strategy of postponing event times has been shown to be less biased than methods that ignore early events (66).

Regardless of the strategy chosen to avoid unstable cumulative incidence estimates in the setting of small risk sets, a minimum risk set size must be chosen. A rule of thumb of using a minimum of 10 cases has been proposed (66). Others have suggested using a cross-validated approach for choosing the minimum risk set (66,69). Guidance is needed on how to implement these strategies when risk sets are small for both exposure groups, as was the case in the current study and will often occur in active comparator studies. Papers that discuss estimating cumulative incidence with small early risk sets have used examples with an unexposed comparator group; for example, pregnancies exposed to a drug compared to pregnancies not exposed to that drug (66,67). The unexposed group is often large enough that no adjustment of the risk set is needed. When both exposure groups require adjustment, it is unknown whether the gestational age at which follow-up should be started or events should be postponed until should be determined independently in each exposure group, or if the gestational age by which both exposure groups have reached the minimum risk set should be used. In the current study, the adjustment was done independently in each group – events were postponed until the gestational age at which the risk set reached 50 women in that exposure group. One might argue that the gestational age should be standardized across exposure groups. More research is needed to determine the optimal method for handling unstable cumulative incidence estimates in active comparator analyses.

CHAPTER 4: METHODS FOR DEFINING THE PREGNANCY COHORT

4.1 Data source and description of the data

Electronic health record (EHR) data from the UNC Health Care system was used for this analysis. The North Carolina Translational and Clinical Sciences Institute (NC TraCS) maintains and stores data from the EHR and makes the data available for research from the Carolina Data Warehouse (CDW).

Data available from the CDW includes diagnosis and procedure codes used for clinical documentation and billing, demographics (age, insurance status, race, ethnicity), patient-reported smoking status, medication orders, clinical measurements, and lab values. For pregnancies, data specific to the pregnancy is recorded under a mechanism of the EHR called a 'pregnancy episode'. All visits associated with prenatal care and delivery should be associated with the pregnancy episode, and data such as last menstrual period (LMP), estimated date of delivery (EDD), and pregravid body mass index (BMI) are recorded in pregnancy episode fields. Similarly, data associated with the delivery were recorded in the delivery episode. Delivery episodes data included the date and time of delivery, the status of the infant (live birth, neonatal demise, fetal demise), birth weight, and gestational age at birth.

4.2 Algorithm for prospective definition of pregnancy timeline

4.2.1 Algorithm overview and rationale

The goal of this project was to assess the risk of pregnancy outcomes with use of antiemetics during pregnancy. To properly estimate cumulative incidence, it is important to study all pregnancies, rather than all live births, or all pregnancies with a documented

pregnancy ending. Observed time for pregnancies that are lost to follow-up contributes to the risk set for outcomes prior to loss.

Secondary administrative data sources often lack a single indicator for pregnancy. Therefore, pregnancy cohorts are assembled by identifying pregnancy outcomes (live birth, stillbirth, miscarriage, termination), and counting back from the outcome date to define the pregnancy period. These strategies exclude pregnancies that do not have observed outcomes in the data source. These pregnancies are still useful in analyses because they contribute to the population at risk and may have documented study outcomes that do not require the pregnancy to end to be determined; for example, a woman diagnosed with preeclampsia at UNC during pregnancy but who later moves and delivers elsewhere should still be included in the analysis of preeclampsia. Similarly, a woman who is followed at UNC until gestational week 35 can still be included in an analysis of miscarriage. Exclusion of pregnancies without documented pregnancy outcomes can result in underestimating the population at risk for all outcomes and the number of outcomes. Therefore, inclusion in the study cohort should be based on evidence of pregnancy, rather than evidence of pregnancy outcome.

To identify women with pregnancies in UNC Health Care EHR data, women with one of the following were identified: 1) a diagnosis or procedure code that is appropriate for early pregnancy, or 2) a pregnancy episode. The list of codes used as “early pregnancy codes” can be found in Appendix Table D.1. The algorithm identifies the earliest early pregnancy code or episode start date during the study period and looks forward in the record for evidence of the end of pregnancy. If no outcome is identified, pregnancies are considered lost to follow-up and the last observed day of pregnancy was defined by the last visit with evidence of an active pregnancy. This process can be repeated to identify multiple pregnancies in a single woman that occur during the study period. The following sections describe steps of the algorithm in detail.

4.2.2 Identifying women eligible for the cohort

Data was requested from the CDW to identify pregnancies using the pregnancy episodes and diagnosis and procedure codes. Pregnancy episodes were not adequate for identifying all pregnancies because early pregnancy losses and terminations were not routinely recorded in the pregnancy episode format. Therefore, diagnosis and procedure codes were also used to identify active pregnancies.

The raw dataset was compiled by pulling all data during the study period, April 4, 2014, through November 30, 2017, for women aged 15-50 years who met one of two eligible criteria: (1) women with an order for one of the antiemetic medications (ondansetron, promethazine, metoclopramide) with an early pregnancy code in the 140 days before or 10 days after the order, and no pregnancy outcome procedure codes (associated with delivery, miscarriage, or termination) within 30 days before the order, or (2) women with a pregnancy episode with an antiemetic order within the first 140 days of pregnancy as defined by the estimated date of delivery in the episode.

Criteria 1 was intended to capture all women with potential for exposure to antiemetics during the first 20 weeks of pregnancy. Women with exposure at the time of a live birth, miscarriage, or termination procedure were excluded to limit the size of the eligible cohort, per request of analysts at CDW. This strategy optimized identification of antiemetic exposed pregnancies while limiting only to women with evidence of antiemetic use that was not given as part of a delivery, miscarriage, or termination procedure. In combination with criteria 2, including all women with a documented pregnancy episode with an antiemetic order during the first 20 weeks of gestation, all women with antiemetic exposure are identified.

For all women meeting the eligibility criteria, the following data was supplied: all pregnancy episode and delivery data during the study period, all diagnosis and procedure codes assigned to the record during the study period, all medication orders during the study period, all

encounters occurring during the study period, and all recordings of smoking status, insurance status, and race/ethnicity associated with encounters during the study period.

4.2.3 Execution of the algorithm

Defining first clinical recognition of pregnancy and pregnancy outcome

Using the list of early pregnancy codes for all eligible women, the first code during the study period was selected for each woman. For women identified only through eligibility criteria 2, with a pregnancy episode with an antiemetic order within the first 140 days of pregnancy, the start date of the pregnancy episode was used instead of the date of the first early pregnancy code. Early pregnancy codes were linked to pregnancy outcomes in the following fashion:

1. *Link early pregnancy codes to pregnancy and delivery episodes.* Pregnancy and delivery episodes were assumed to be the most accurate source of pregnancy outcome data because outcomes, delivery dates, and gestational age were entered directly into the EHR and do not need to be approximated using diagnosis and procedure codes. A description of how pregnancy and delivery episodes were cleaned for analysis is included in Appendix A.
    a. *Criteria for linkage:* early pregnancy code date is between 2 weeks after the pregnancy start date (EDD-266 days) and the pregnancy outcome date
2. *Link early pregnancy codes to pregnancy episodes without delivery episodes.* Some pregnancies episodes did not have corresponding delivery episodes due to loss to follow-up or lack of formal recording of the pregnancy outcome. In these cases, the EDD was used to define the start of pregnancy and diagnosis and procedure codes were used to define the pregnancy outcome date and type. The process for defining pregnancy outcomes using diagnosis and procedure codes is described in Appendix A. If no pregnancy outcome was defined using diagnosis and procedure codes, the pregnancy was retained and considered lost to follow-up.

a. *Criteria for linkage:* early pregnancy code date is between 2 weeks after the pregnancy start date (EDD-266 days) and the pregnancy outcome date. If the pregnancy is lost to follow-up and the pregnancy outcome date is undefined, the early pregnancy code date must be between 2 weeks after the pregnancy start date and the end of the pregnancy episode or the EDD, whichever is first.

3. *Link early pregnancy codes to diagnosis and procedure codes for pregnancy outcomes:* when an early pregnancy code does not link to a pregnancy episode, the outcome of pregnancy can still be defined by linking to diagnosis and procedure codes that indicate pregnancy outcomes. The process for defining pregnancy outcomes using diagnosis and procedure codes is described in Appendix A. If no pregnancy outcome was defined using diagnosis and procedure codes, the pregnancy was retained and considered lost to follow-up.
    a. *Criteria for linkage:* diagnosis or procedure code is between the date of the early pregnancy code and 286 days after the early pregnancy code (286 days was chosen assuming the early pregnancy code would be identified at the earliest point of 14 days of gestation and the outcome could occur through 43 weeks (301 days) of gestation)

Assigning gestational age

After linkage of early pregnancy codes and pregnancy episodes to pregnancy outcomes, gestational age was defined using EDD from the pregnancy episode or using diagnosis codes that indicate gestational age. EDD was determined using LMP dates and confirmed by first trimester ultrasound, when available. The start of pregnancy was estimated by subtracting 280 days from the EDD. Gestational age of the pregnancy outcome and early pregnancy indicator code was calculated by subtracting the pregnancy start date from date of each event.

For pregnancies without an EDD, gestational age was classified using diagnosis codes that indicate gestational age. ICD-10 codes that indicate specific gestational weeks were prioritized over codes that were less specific. For pregnancies with outcomes defined, the closest gestational age code to the outcome date was used to define gestational age. For pregnancies without outcomes defined, the closest gestational age code within 20 days prior to the early pregnancy code was used to define gestational age. Only gestational age codes on or prior to the date of the early pregnancy code was used for pregnancies without outcomes to avoid conditioning on the future beyond the early pregnancy code date for inclusion in the cohort. If multiple codes were listed on the same day, the code suggesting the shortest duration was selected. All gestational age codes and their assigned durations are listed in Appendix Table D.2. The duration assigned to the selected code was used to calculate a start of pregnancy by subtracting the duration from the date of the code.

For all remaining pregnancies without gestational age, medical record review was completed to abstract gestational age.

Defining multiple pregnancies per woman

After the first pregnancy was defined for each woman in the cohort, the algorithm defines any subsequent pregnancies during the study period. If no pregnancy outcome was defined after the first iteration of the algorithm, the next early pregnancy code is selected. If a pregnancy outcome was defined in the first iteration, the next early pregnancy code that occurs at least 60 days after the pregnancy outcome date is selected. A 60-day gap between pregnancy outcome and identification of a subsequent pregnancy was chosen to avoid incorporating codes from postpartum visits as evidence of the start of a new pregnancy. The next pregnancy is then defined by looping through the steps outlined above using the new early pregnancy code. This process continues until there are no eligible early pregnancy codes left during the study period.

After the final algorithm loop, the pregnancy cohort is cleaned to include a pregnancy start date and last day of pregnancy for each pregnancy. If a pregnancy outcome was identified,

the last day of pregnancy is defined as the outcome date. If no pregnancy outcome was identified, the pregnancy is considered lost to follow-up and the last day of follow-up is defined as the last visit with evidence of ongoing pregnancy before the expected EDD, before a visit labeled ‘postpartum’, or before the start of a subsequent pregnancy for the same woman. Overlapping pregnancies were remedied in the following ways: (1) if the first pregnancy had a defined outcome and the second pregnancy had gestational age estimated by diagnosis and procedure codes, the start date of the second pregnancy was moved to one day after the outcome date of the first pregnancy, and (2) if the first pregnancy does not have an outcome date, the last possible day of the first pregnancy was moved to one day before the start date of the second pregnancy, and the last visit with evidence of ongoing pregnancy was defined as the last day of pregnancy.

Final pregnancy cohort

All pregnancies with less than one day of follow-up were excluded from the cohort. This includes pregnancies that were identified on the day of their outcome or on the day they were classified as lost to follow-up; i.e. pregnancies that were only seen at UNC once. These pregnancies do not contribute any person-time to survival analyses and therefore are excluded. Pregnancies that were first identified after 140 days of gestation were also excluded because the study exposure period was in the first 140 days and these pregnancies were not observed in that period. Ectopic and molar pregnancies were also excluded from the cohort. These pregnancies cannot develop into healthy pregnancies and therefore are not at risk for miscarriage, stillbirth, or other late study outcomes. Multiple gestation pregnancies were also excluded from analyses since they have different risk factors for the study outcomes.

4.2.4 Validation of pregnancy outcomes

Review of medical records was used to verify outcomes assigned by the algorithm. The algorithm was not designed to be generalizable and reusable in other EHR data settings, but rather prioritized any evidence of key pregnancy outcomes (miscarriage and stillbirth) to identify

all possible cases (see Appendix A for details). Using this approach, it is unlikely that miscarriage and stillbirth cases are misclassified as live births, but cases classified as miscarriages and stillbirths may be misclassified. Therefore, records were reviewed to verify outcome types and dates for the following outcomes: miscarriage, stillbirths, and terminations.

Two reviewers extracted the following data from the medical record: outcome type (miscarriage, termination, stillbirth, live birth, ectopic or molar pregnancy, or not pregnant), outcome date, and gestational age (LMP, EDD, or gestational age at the outcome date). For miscarriage cases, the outcome date was assigned as the date the miscarriage was confirmed in a clinical setting. Clinical confirmation was determined by ultrasound report or by patient report of passed products of conception if no ultrasound was completed. For termination cases, the outcome date was assigned as the date of medical or surgical termination. For stillbirth cases, the outcome date was assigned as the date of birth.

4.3 Defining antiemetic groups

The pregnancy algorithm was executed irrespective of antiemetic orders. After all pregnancies were defined with pregnancy start dates, antiemetic orders that occurred between gestational weeks 2 (conception) and 20, or days 15-140, were identified. For the primary analysis in both aims, antiemetic exposure group was assigned based on the first eligible prescription received in pregnancy (the first prescription received of the study antiemetics of ondansetron, metoclopramide, or promethazine). If a woman received prescriptions for eligible antiemetics in both study groups on the first day she received any antiemetic prescription, her pregnancy was excluded from the analysis.

4.4 Defining covariates

Covariates were defined using records occurring at or before the first eligible antiemetic prescription. Maternal age was defined at the start of pregnancy. Race and ethnicity data were available in records of encounters in the EHR and may reflect self-identified or staff identified categories. These categories are white, black, and other, consisting of Asian, American Indian

or Alaska Native, Native Hawaiian or other Pacific Islander. Insurance status was defined by the payment type used at the encounter of the first eligible antiemetic order (public, private, or self-pay). Smoking status (current, former, or never) was defined using encounter data for the period between pregnancy start and the first eligible antiemetic order.

Comorbidities were defined using diagnosis and procedure codes in the record on or prior to the date of first eligible antiemetic prescription. The following comorbidities were defined: asthma, renal disease, depression, other mental health disorders, hypertension, sleep disorders, diabetes, seizure disorders, alcohol abuse, drug abuse, and classification as a high-risk pregnancy. The diagnosis codes used to define these comorbidities are in Appendix Table D.9.

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. The following categories of medications were defined: analgesics, anticonvulsants, antipsychotics, benzodiazepines, NSAIDs, antidepressants, PPIs, antihypertensives, insulin, and opioids. Prenatal vitamin orders were included from 60 days prior to pregnancy start until the first eligible antiemetic order to include use among women who were planning for pregnancy.

Pregravid body mass index 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 to approximate pregravid BMI.

Proxies of nausea and vomiting severity included any hospitalization or emergency room visit for HEG, the care setting for first eligible antiemetic prescription, the administration method of the antiemetic, and prescriptions for antiemetics other than ondansetron, metoclopramide, and promethazine. Alternative antiemetics included doxylamine/pyridoxine, antihistamines and dopamine antagonists other than promethazine and metoclopramide, and scopolamine patches.

CHAPTER 5: ONDANSETRON USE IN EARLY PREGNANCY AND THE RISK OF MISCARRIAGE

5.1 Introduction

Ondansetron is a 5-HT_3-receptor antagonist that prevents nausea and vomiting and is approved for use with chemotherapy, radiation therapy, and after surgery. Use of ondansetron, while off-label, has been recommended by the American College of Obstetricians and Gynecologists for hyperemesis gravidarum (HEG) and severe nausea and vomiting that is unresponsive to other recommended therapies (27). However, a recent utilization study suggests ondansetron is prescribed beyond severe cases; more than 20% of pregnant women filled a prescription for ondansetron in the US in 2014, which represents a dramatic increase in use since becoming available in generic form in 2007 (3). Nausea symptoms typically peak between weeks 9 and 12 (18), therefore treatment occurs during the vulnerable early weeks of pregnancy, prompting safety concerns.

Available studies on the risk of miscarriage with ondansetron use in early pregnancy have reported strong inverse associations of ondansetron compared to non-users (5,9,14) and a modest decreased risk compared to users of alternative antiemetics (5). Analyses that rely upon non-user comparison groups are confounded by the well-established inverse association of nausea and vomiting with miscarriage (18,19,22). The underlying mechanism for the association between nausea and vomiting and miscarriage is unclear, but has been hypothesized to be due to avoidance of risk factors, effects of human chorionic gonadotropin, or effects of other hormones (2). Regardless of mechanism, lower risk of miscarriage among women with nausea and vomiting will also result in lower risk of miscarriage among women treated with antiemetics when compared to a population of untreated women who are mostly

free from nausea and vomiting. Therefore, confounding by nausea and vomiting must be addressed to evaluate the any potential effect of an antiemetic drug on the risk of miscarriage. While previous studies have controlled for hospitalizations due to nausea and vomiting or HEG and use of other antiemetics, these measures are crude approximations of symptom severity. The possibility remains that the strong inverse association of nausea and vomiting with miscarriage obscures a true elevated risk of miscarriage with ondansetron use. In absence of data collected on nausea and vomiting frequency and severity, use of an active comparator group comprised of women with a similar indication treated with alternative antiemetic medications is necessary to control for confounding by nausea and vomiting. Prior results using an active comparator are limited by a lack of data to assess comparability of antiemetic groups or clear differences in nausea and vomiting severity between groups (5).

The objective of this study was to estimate the risk of miscarriage among ondansetron-exposed women compared with a group of women using alternative antiemetic medications, specifically promethazine or metoclopramide.

5.2 Methods

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 EHR software (Verona, WI) to standardize records across the system. We used records for 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.

Identifying pregnancies

Pregnancies were defined in a prospective fashion by identifying the first clinical encounter with recognition of pregnancy using a list of diagnosis and procedure codes that are expected in the first half of pregnancy (code list in Appendix Table D.1), or the initiation of a pregnancy event in the Epic EHR system. From this date of first pregnancy recognition, pregnancies were followed forward for evidence of a pregnancy outcome. If no outcome was identified, pregnancies were considered lost to follow-up at the last visit with evidence of an active pregnancy. Gestational age was defined using last menstrual period dates or ultrasound dating as recorded in standardized fields in the EHR. For pregnancies without gestational age, 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 during the study period. Ectopic pregnancies, molar pregnancies, and 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.

Antiemetic exposure

Antiemetic exposure was defined using prescription orders. Women with prescriptions 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 (27). These drugs have historically been widely used during pregnancy in the US (3,70), however recently have decreased in use due to the availability of ondansetron in generic form and it's more favorable side effect profile

(3,29). 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.

Prescriptions 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, and administered prescriptions included all medications taken by the patient in a health care facility, including intravenous medications.

Miscarriage and termination definitions

Miscarriage was defined as fetal loss before 20 weeks of gestation. Potential miscarriage cases were identified using delivery records of fetal demise and diagnosis codes and procedure codes indicating miscarriage, or prescriptions for drugs used in medication abortion procedures (code list in Appendix Table D.3). Medical records for all potential miscarriages were reviewed to confirm the outcome and outcome date. The date at which the miscarriage was confirmed in a clinical setting was used as the outcome date. Clinical confirmation was determined by ultrasound report or by patient report of passed products of conception if no ultrasound was completed.

Termination of pregnancy was defined as elective surgical or medical termination, regardless of indication. Terminations were identified using diagnosis and procedure codes (code in list Appendix Table D.4). Medical records for all potential terminations were reviewed to confirm outcome type and date.

Covariates

Covariates were defined using records occurring at or before the first eligible antiemetic prescription (Figure 5.1). Maternal age was defined at the start of pregnancy. Race and ethnicity were classified as white, black, and other (Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander). Insurance status was defined by the payment type used at

the encounter of the first eligible antiemetic order (public, private, or self-pay). Smoking status (current, former, or never) was defined using encounter data for the period between pregnancy start and the first eligible antiemetic order.

Proxies of nausea and vomiting severity were measured prior to the first eligible antiemetic prescription and included any hospitalization or emergency room visit for HEG, the care setting for first eligible antiemetic prescription, the type of prescription for the antiemetic (written or administered), and prescriptions 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 prescription (conditions and code list in Appendix Table D.9). 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 to allow for refills that extend into the pregnancy period. Prenatal vitamin orders were included from 60 days prior to pregnancy start until the first eligible antiemetic order. Pre-pregnancy 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.

Statistical analysis

Data were missing for race (1.3%), ethnicity (1.9%), smoking status (1.8%), and pre-pregnancy BMI (11.7%). Multiple imputation by chained equations was used to impute values for these variables (71). Five datasets were imputed and results were summarized over the imputed datasets using Rubin's rules (72).

Measured confounding was controlled using stabilized inverse probability of treatment (IPT) weights (73). Propensity scores were estimated with multivariable logistic regression.

Asymmetric trimming of the propensity scores was completed to minimize the impact of large weights due to women being treated contrary to prediction; women with propensity scores less than the first percentile of ondansetron exposed women or with propensity scores greater than the 99th percentile of comparator exposed women were excluded and propensity scores were recalculated after these exclusions (74). Absolute standardized mean differences between antiemetic groups were calculated for all covariates and differences <0.1 were considered balanced (75).

The timescale was gestational age in days and the cumulative incidence of miscarriage was calculated at the end of the risk period at 20 weeks (140 days). A pregnancy entered the analysis two days after the first eligible antiemetic prescription and remained in the risk set until miscarriage, termination, or censoring due to loss to follow-up or 140 days of gestation. Follow-up was started two days after the antiemetic order to avoid attributing events that occur during the same health care encounter but billed on different days to the antiemetic. The main analysis followed an intent-to-treat design and changes in antiemetic prescribing after the first eligible prescription were ignored. Pregnancies that ended in elective termination were considered competing events. Figure 5.1 illustrates the pregnancy timeline.

Survival analysis methods were used to estimate the association between antiemetic agent and miscarriage. The cumulative incidence of miscarriage was estimated in each antiemetic group using the Fine and Gray method for competing events (60), modified to account for varied entry times (61), and weighted to control for measured confounding. This method estimates cumulative incidence while accounting for time of entry into the cohort and competing events by adjusting the size of the risk set based on the gestational age of entry and the gestational age of censoring or competing events (61). Risk differences (RD) and risk ratios (RR) were calculated by subtracting or dividing the cumulative incidence in ondansetron group by the cumulative incidence in the comparator group at 140 days of gestation using the unweighted and IPT-weighted estimator (76).

To calculate confidence intervals for RR and RD estimates that account for correlated observations among women with multiple pregnancies and to adequately account for varied entry times and competing events, we conducted 1000 nonparametric bootstrapped samples with replacement (63). The empirical 95% confidence intervals were estimated using the 2.5th and 97.5th percentiles of the distribution.

Women enter the analysis at two days after the gestational age of their first eligible antiemetic prescription; therefore, the population at risk of miscarriage grows with gestational age. Miscarriage events that occur early in gestation when the population at risk is small can artificially inflate the cumulative incidence estimate because the denominator is small (66). To limit the influence of early events, we postponed event times for miscarriage and termination events that occurred when the population at risk was smaller than 50 pregnancies. This strategy of postponing event times has been shown to be less biased than methods that ignore early events (66). This method also does not change the interpretation of results, unlike methods that exclude early events by starting follow-up only once the risk set has reached a certain size. Postponing event times allows for estimation of cumulative incidence based on all observed cases. For comparison, results without postponing event times were also estimated.

Analyses were completed using the mice, mstate, and boot packages in R, version 3.5.3 (77–80).

Per-protocol analysis

Exposure misclassification is possible when defining exposure status by the first eligible antiemetic received in pregnancy. Women may receive subsequent prescriptions for alternative antiemetics if symptom control is not achieved. To account for this potential bias, a per-protocol analysis was completed by censoring pregnancies at the time of a prescription of an antiemetic from the other exposure group (65). This analysis estimates the comparative risk of exposure to only one of the two antiemetic groups under study.

Sensitivity analyses

To address possible exposure misclassification due to lack of consumption of written prescriptions for antiemetics, the exposure definition was limited to administered prescriptions (administered analysis). To account for a latency period between the start and clinical recognition of miscarriage, the start of follow-up for miscarriage was delayed until 23 days after the gestational age of the prescription (latency analysis). The 23-day latency period is informed by a study with repeat ultrasounds among women with miscarriage which reported a median of 23 days between arrest of development and miscarriage diagnosis (81).

Additionally, we assessed the impact of selection bias due to loss to follow-up by simulating two possible scenarios for pregnancies lost to follow-up before 20 weeks. It is reasonable to assume that a woman will not return for pregnancy-related care if the pregnancy ends in miscarriage or termination, therefore an association between being lost to follow-up and the outcome of miscarriage is possible. All pregnancies that were lost to follow-up were reclassified as miscarriage cases using the gestational age of last follow-up as the gestational age of miscarriage. We also assessed a scenario that assumes all pregnancies lost to follow-up survived until 20 weeks but were unobserved because they received care outside of UNC. All pregnancies that were lost to follow-up were reclassified as surviving pregnancies without miscarriage and were administratively censored at 140 days of gestation.

5.3 Results

We identified 3241 pregnancies with antiemetic orders in the first 140 days of gestation. 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. Women with ondansetron and comparator antiemetics prescribed on the same day, multiple gestations, and ectopic or molar pregnancies were also excluded. The final analysis population included 1712 ondansetron-exposed women and 908 comparator exposed women, which further

excluded pregnancies that experienced events or were lost to follow-up within two days of the antiemetic prescription. Inclusion of pregnancies in the analysis is detailed in Figure 5.2.

Characteristics of the first eligible antiemetic order received during pregnancy are described in Table 5.1. Comparator antiemetics were more likely to be given intravenously and in an emergency room setting than ondansetron, while ondansetron was more likely to be given in an inpatient setting. The median gestational age at first eligible antiemetic order was 63 days (interquartile range (IQR): 50-86) in the ondansetron group and 67 days (IQR: 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%). Few other differences in demographics, comorbidities, and concurrent medications were observed between groups (Table 5.1). After propensity score weighting, groups were similar on all variables included in the propensity score with absolute standardized mean differences less than 10%. After record review of miscarriage cases identified using delivery records and diagnosis and procedure codes, 95 miscarriage cases remained eligible for analysis.

Results for the main analysis, per-protocol analysis, and sensitivity analyses are presented in Table 5.2. The unweighted cumulative incidence of miscarriage was 13.0% (95% CI 4.9, 32.1) in the ondansetron group and 8.9% (95% CI 2.7, 21.8) in the comparator group. IPT-weighted cumulative incidence curves for miscarriage in each antiemetic group are presented in Figure 5.3. After weighting for measured confounders, no evidence of an association between antiemetic received and miscarriage was observed in the main analysis (RR 1.23, 95% CI 0.23, 8.51; RD 2.3% 95% CI -25.4, 24.1). Results were consistent across the per-protocol analysis, which accounted for women who were exposed to both antiemetic groups (RR 1.31, 95% CI 0.25, 9.85; RD 3.0% 95% CI -24.7, 26.5). Results for the additional sensitivity analyses (the administered analysis, the 23-day latency analysis, and in both lost to follow-up

analyses) were consistently close to the null and did not offer evidence that key design and analysis assumptions impacted results.

5.4 Discussion

In this analysis of women initiating antiemetics during the first 20 weeks of pregnancy, we did not find evidence of a difference in risk of miscarriage in ondansetron-exposed women compared with promethazine or metoclopramide exposed women. After considering multiple threats to validity through sensitivity analyses, results were largely unchanged.

Previous studies have not reported an increase in risk of miscarriage with ondansetron use, but differences in study design and lack of reporting on comparator antiemetic groups makes direct comparison of results difficult. A study using the Danish registries reported a strong inverse association of ondansetron with miscarriage when compared to non-users and an attenuated inverse association as compared to users of antihistamine antiemetics (5). Both the non-user analysis and the antihistamine comparator analysis are likely confounded by nausea and vomiting severity. Ondansetron was used by 0.3% of pregnant women in Denmark at the time of the analysis. If ondansetron is reserved for HEG or used later in gestation as a last resort therapy, the risk of miscarriage in ondansetron users would likely be lower than in other antiemetic groups because the underlying risk of miscarriage is higher at early gestations. In our study, the distribution of gestational age at first eligible antiemetic order was very similar between exposure groups. Previous studies have not reported this information for both antiemetic groups, therefore we cannot rule out the possibility that utilization patterns differed between antiemetics.

By capturing all ondansetron, promethazine, and metoclopramide prescriptions during early pregnancy across a health care system, we were able to assemble a cohort that incorporated a range of symptom severities, enhancing the generalizability of our findings. Compared to previous cohorts that included populations where all or most were hospitalized for HEG (5,14), our cohort had a much lower rate of hospitalization (<2% in both antiemetic

groups). While many women in our cohort were seen in the emergency room for nausea and vomiting symptoms (44% in the ondansetron group and 52% in the comparator group), this likely reflects care seeking behaviors as well as symptom severity. Accordingly, 44% of patients in our cohort with an antiemetic prescribed in an outpatient setting had public insurance (Medicaid) or no insurance at the time of the order, compared to 74% of those with an antiemetic prescribed in the emergency room. There were more intravenous administrations in the comparator antiemetic group than the ondansetron group suggesting more severe cases in the comparator groups; however, this difference was balanced after weighting. Consistency in timing of first eligible antiemetic prescription between groups suggests a similarity in utilization patterns of these drugs for treating nausea and vomiting in pregnancy.

A strength of our study is the prospective identification of pregnancies and use of advanced survival analysis methods to analyze the appropriate population at risk for miscarriage. Pregnancies were followed from two days after the gestational age of their first eligible antiemetic prescription without conditioning on future events. This allows for proper specification of the denominator for miscarriage cases by including pregnancies at risk at a given gestational age, including those that are eventually lost to follow-up or end in elective termination (62). Use of EHR data is advantageous for this type of analysis because of the availability of gestational age and delivery data, and the option to review records when key details were missing.

We took several measures to avoid incorrectly attributing miscarriage cases to antiemetic exposure when reverse causation was possible. We reviewed medical records to confirm both the accuracy of the miscarriage classification and the date of clinically confirmed miscarriage. Women that received prescriptions for antiemetics on or after the confirmed miscarriage date dropped out of the analysis once miscarriage cases were updated and the timing of clinical recognition was corrected. We attempted to account for a latency period between miscarriage onset and clinical recognition. A limitation of our data is a lack of

information on when a miscarriage started because early ultrasounds are not routinely conducted to confirm viability at early gestational ages. Failure to account for imperfect miscarriage dating and the period during which miscarriage is in progress but not detected can result in artificially inflated miscarriage risk in each antiemetic group. We adjusted for potential misclassification using recent data from a study with early ultrasounds that estimated the median period between arrest of development and diagnosis of miscarriage (81). However, this is a crude approximation of the true latency period for cases in our study.

A notable limitation of this study is use of prescription orders rather than prescription fills or patient report of medication use to define antiemetic exposure groups. After restricting to antiemetics administered during a healthcare encounter and therefore likely to be consumed by the patient, we did not observe a difference in risk of miscarriage between antiemetic groups. The per-protocol analysis also produced similar results of no difference in risk of miscarriage. Conclusions from the per-protocol analysis may have been strengthened with inclusion of time-varying covariates that are associated with receipt of a second prescription such as nausea and vomiting symptom severity and side effects (65), however such detailed information is not reliably recorded in structured fields in the EHR. We are also limited by small sample sizes, especially in sensitivity analyses. The study period was limited to data available in the current EHR system, which started in April 2014. An additional limitation is the inability to see care received at facilities outside of the UNC system. Misclassification of antiemetic exposure status and covariates is possible in this setting. However, given similarities between groups in timing of first eligible antiemetic exposure and the care setting of the first eligible antiemetic order, and balance seen in nearly all comorbidities and concomitant medications in the unweighted data, we do not expect missing covariate data to differ substantially between groups. The proportion of women lost to follow-up was not small, however it was similar between antiemetic groups. After assuming the extremes of the outcome status for all women lost to follow-up, we observed no difference in results. Future research would be improved by making use of EHR data linked

to insurance claims data, which combines the availability of gestational age and delivery records in EHR with prescription fills and care received at multiple institutions from claims data.

Finally, early events that occur when the risk set is small can have a large impact on estimates of cumulative incidence. Cumulative incidence estimates from the 23-day latency period analysis were inflated to unreasonable estimates for miscarriage due to small numbers of women in the risk set (see Appendix Table B.1 for results). We based our method of postponing event times on previously published work that explores methods for handling early events in pregnancy studies (66). More work is needed to evaluate methods for handling early pregnancy events and exposures while also considering confounding and loss to follow-up.

In summary, we observed no evidence of a difference in risk of miscarriage between women exposed to ondansetron during early pregnancy and women exposed to promethazine or metoclopramide in this cohort of pregnancies treated for nausea and vomiting symptoms. These results address a previously unexplored yet clinically relevant research question of whether risk of miscarriage differs between women treated for nausea and vomiting with different antiemetics, can help inform treatment decisions for pregnant women, and offer evidence that ondansetron does not increase risks.

Table 5.1. Characteristics of pregnant women seen at UNC Health Care between 2014-2017 with antiemetic exposure by antiemetic exposure status

	Unweighted			IPT-Weighted, trimmed
	Ondansetron (N=1712)	**Comparators (N=908)**	**Absolute standardized difference[1]**	**Absolute standardized difference[1]**
Age in years at start of pregnancy, mean (SD)	27.5 (6.0)	27.4 (5.8)	0.01	0.01
Insurance status, N (%)				
Private insurance	715 (41.8)	347 (38.2)	0.07	0.02
Public insurance	711 (41.5)	406 (44.7)	0.06	0.02
No insurance	286 (16.7)	155 (17.1)	0.01	0.00
Race, N (%)				
White or Caucasian	820 (47.9)	421 (46.4)	0.03	0.01
Black or African American	531 (31.0)	313 (34.5)	0.08	0.02
Other	339 (19.8)	161 (17.7)	0.06	0.03
Missing	22 (1.3)	13 (1.4)		
Hispanic, N (%)	258 (15.1)	122 (13.4)	0.05	0.03
Missing	33 (1.9)	17 (1.9)		
Smoking status, N (%)				
Current smoker	362 (21.1)	206 (22.7)	0.03	0.02
Former smoker	225 (13.1)	128 (14.1)	0.03	0.02
Never smoker	1094 (63.9)	558 (61.5)	0.05	0.03
Missing	31 (1.8)	16 (1.8)		
Comorbidities, N (%)				
Asthma	118 (6.9)	81 (8.9)	0.08	0.01
Renal disease	25 (1.5)	17 (1.9)	0.03	0.01
Depression	227 (13.3)	119 (13.1)	0.00	0.01
Other mental health disorders	246 (14.4)	132 (14.5)	0.00	0.01
Hypertension	118 (6.9)	87 (9.6)	0.10	0.02
Sleep disorders	36 (2.1)	19 (2.1)	0.00	0.02
Diabetes	48 (2.8)	34 (3.7)	0.05	0.00
Seizure disorders	38 (2.2)	22 (2.4)	0.01	0.01
Alcohol abuse	10 (0.6)	6 (0.7)	0.01	0.00
Drug abuse	91 (5.3)	56 (6.2)	0.04	0.01
High risk pregnancy	292 (17.1)	161 (17.7)	0.02	0.01
Pre-pregnancy BMI, N (%)				
Underweight or normal (<24.9)	644 (37.6)	291 (32.1)	0.07	0.01
Overweight (25 to <30)	375 (21.9)	197 (21.7)	0.02	0.01
Obese (30 or greater)	520 (30.4)	286 (31.5)	0.05	0.01
Missing	173 (10.1)	134 (14.8)		
Concomitant medications, N (%)				
Prenatal vitamins	249 (14.5)	161 (17.7)	0.09	0.02
Analgesics	479 (28.0)	257 (28.3)	0.01	0.01
Anticonvulsants	25 (1.5)	21 (2.3)	0.06	0.00
Antipsychotics	23 (1.3)	21 (2.3)	0.07	0.00
Benzodiazepines	27 (1.6)	20 (2.2)	0.05	0.00

	Unweighted			IPT-Weighted, trimmed
	Ondansetron (N=1712)	**Comparators (N=908)**	**Absolute standardized difference[1]**	**Absolute standardized difference[1]**
Concomitant medications, N (%), continued				
NSAIDs	132 (7.7)	54 (5.9)	0.07	0.06
Antidepressants	81 (4.7)	33 (3.6)	0.05	0.00
Proton-pump inhibitors	46 (2.7)	23 (2.5)	0.01	0.02
Antihypertensives	20 (1.2)	16 (1.8)	0.05	0.02
Insulin	16 (0.9)	13 (1.4)	0.05	0.01
Opioid	244 (14.3)	131 (14.4)	0.01	0.02
Health care utilization at UNC (1 or more visits before antiemetic order), N (%)				
Emergency room visit	882 (51.5)	523 (57.6)	0.12	0.02
Inpatient visit	115 (6.7)	44 (4.8)	0.08	0.01
Outpatient visit	1044 (61.0)	498 (54.8)	0.12	0.00
Pregnancy-related care at or before antiemetic order, N (%)				
Prenatal care visit	717 (41.9)	347 (38.2)	0.07	0.01
Maternal/fetal medicine (high-risk) visit	233 (13.6)	143 (15.7)	0.06	0.00
UNC Health Care System hospital of antiemetic order, N (%)				
Caldwell, Chatham, Lenoir, or Pardee	146 (8.5)	80 (8.8)	0.01	0.01
High Point Regional	235 (13.7)	127 (14.0)	0.01	0.00
Johnston	126 (7.4)	116 (12.8)	0.18	0.00
Rex	176 (10.3)	210 (23.1)	0.35	0.00
UNC Hospitals	1029 (60.1)	375 (41.3)	0.38	0.01
Year, N (%)				
2014	402 (23.5)	71 (7.8)	0.44	0.00
2015	414 (24.2)	151 (16.6)	0.19	0.03
2016	511 (29.8)	377 (41.5)	0.25	0.02
2017	385 (22.5)	309 (34.0)	0.26	0.01
Care setting of antiemetic order, N (%)				
Emergency	744 (43.5)	471 (51.9)	0.17	0.02
Inpatient	107 (6.2)	43 (4.7)	0.07	0.02
Outpatient	861 (50.3)	394 (43.4)	0.14	0.01
Administration of antiemetic, N (%)				
Inpatient administration	720 (42.1)	424 (46.7)	0.09	0.02
Intravenous administration	426 (24.9)	365 (40.2)	0.33	0.00
Orders for other antiemetics, N (%)	233 (13.6)	261 (28.7)	0.38	0.01

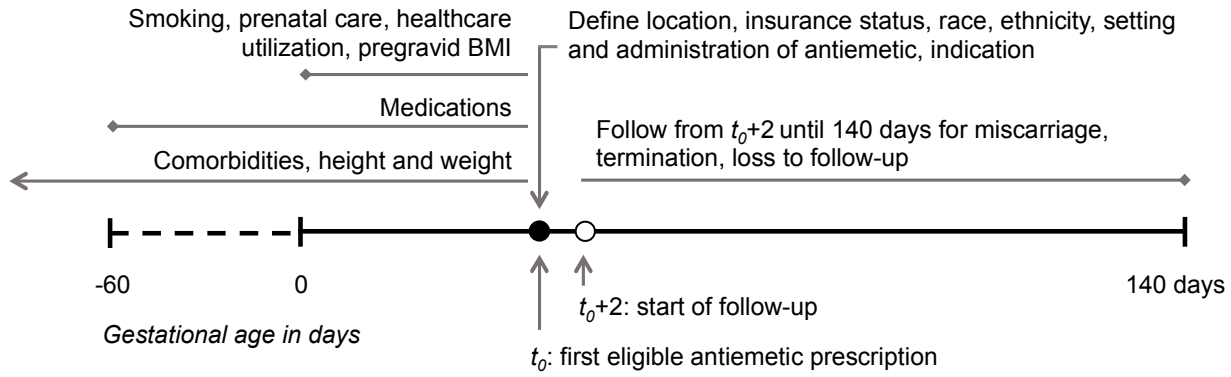
	Unweighted			IPT-Weighted, trimmed
	Ondansetron (N=1712)	**Comparators (N=908)**	**Absolute standardized difference[1]**	**Absolute standardized difference[1]**
Indications for antiemetics, N (%)				
Nausea and vomiting	556 (32.5)	365 (40.2)	0.16	0.02
HEG (inpatient)	22 (1.3)	13 (1.4)	0.01	0.02
HEG (emergency)	279 (16.3)	178 (19.6)	0.09	0.01

Table 5.2. Risk of miscarriage at 140 days among pregnant women seen at UNC Health Care between 2014-2017 with ondansetron or comparator antiemetic exposure

			RD (95% CI) (%)		RR (95% CI)	
	N cases / N total	**Unweighted cumulative incidence (%)[1]**	**Unweighted**	**Weighted**	**Unweighted**	**Weighted**
Main analysis						
Ondansetron	64 / 1712	13.0% (4.9, 32.1)	4.1% (-11.8, 25.4)	2.3% (-25.4, 24.1)	1.46 (0.37, 6.80)	1.23 (0.23, 8.51)
Comparators	31 / 908	8.9% (2.7, 21.8)	0	0	1	1
Per-protocol						
Ondansetron	64 / 1708	13.7% (5.3, 33.9)	5.6% (-9.3, 28.2)	3.0% (-24.7, 26.5)	1.70 (0.46, 7.95)	1.31 (0.25, 9.85)
Comparators	30 / 903	8.0% (2.3, 20.6)	0	0	1	1
Administered						
Ondansetron	39 / 720	16.1% (5.5, 47.6)	6.4% (-21, 41.7)	1.1% (-30.6, 38.4)	1.66 (0.3, 15.54)	1.09 (0.21, 16.40)
Comparators	13 / 424	9.7% (1.4, 34.9)	0	0	1	1
23-day latency						
Ondansetron	27 / 1463	11.3% (2.8, 80.1)	4.2% (-51.8, 65.6)	1.8% (-69.7, 61.1)	1.58 (0.14, 19.61)	1.21 (0.08, 40.66)
Comparators	14 / 758	7.1% (1.2, 73.8)	0	0	1	1
All LTFU as miscarriage cases						
Ondansetron	279 / 1712	31.8 (21.6, 49.7)	0.1 (-26.5, 21.6)	3.4 (-28.4, 26.6)	1.00 (0.47, 1.91)	1.12 (0.50, 2.39)
Comparators	170 / 908	31.7 (20.6, 56.9)	0	0	1	1
All LTFU as non-cases						
Ondansetron	64 / 1712	12.7 (4.7, 31.8)	4.2 (-11.4, 25)	2.2 (-25.1, 23.8)	1.49 (0.37, 7.11)	1.24 (0.23, 8.57)
Comparators	31 / 908	8.5 (2.5, 21.4)	0	0	1	1

[1]Estimated using the Fine and Gray method accounting for varied entry times `(61)

Figure 5.1. Illustration of the pregnancy timeline



Legend: The pregnancy timeline uses gestational age in days as the timescale. Follow-up starts at 2 days after t_0, the gestational age at the first eligible antiemetic prescription. Pregnancies are followed from t_0 +2 until miscarriage, termination, loss to follow-up, or 140 days. Covariates are defined at or before the gestational age of the first eligible antiemetic order.

Figure 5.2. Inclusion and exclusion of pregnancies seen at UNC Health Care between 2014-2017 with ondansetron or comparator antiemetic exposure in the analysis

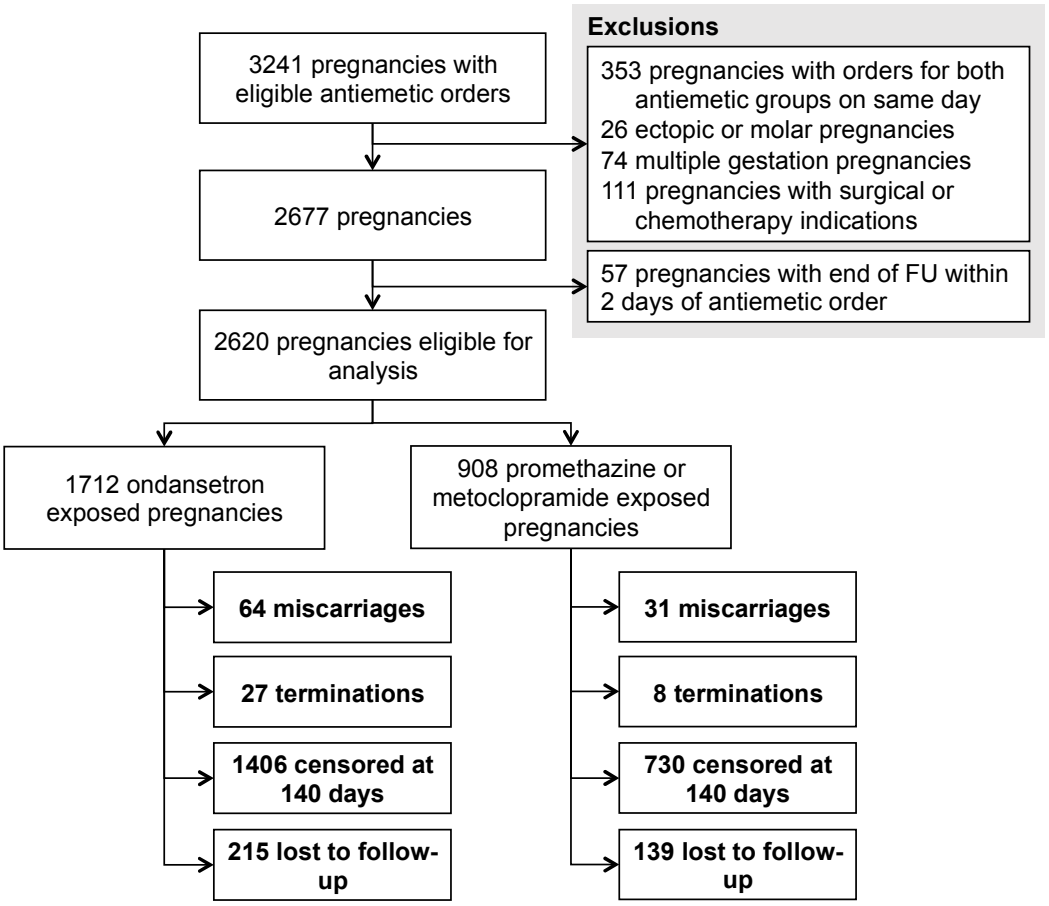
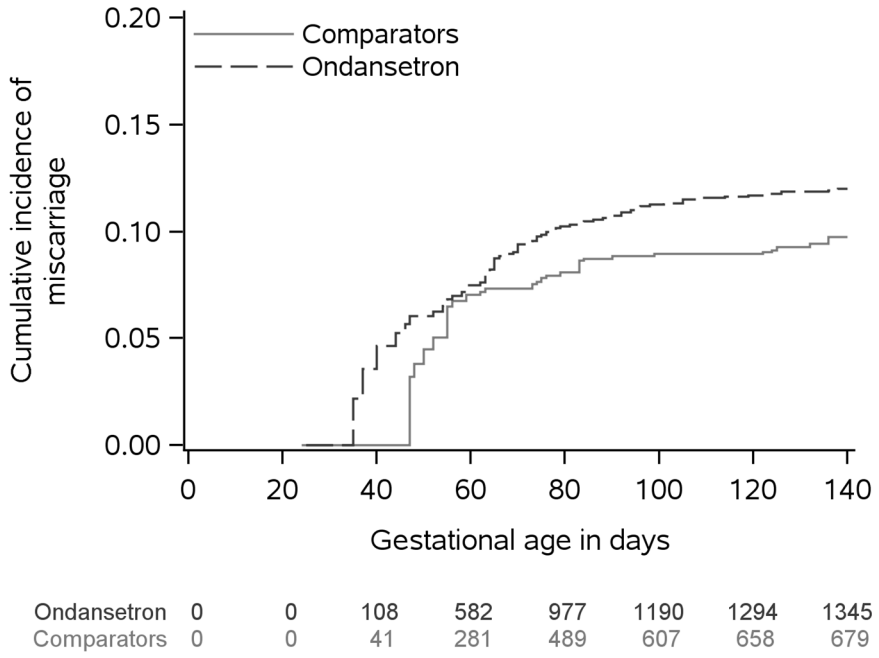


Figure 5.3. Cumulative incidence of miscarriage by antiemetic group, accounting for confounding using IPT-weights



Legend: Cumulative incidence curves were estimated using the Fine and Gray estimator that was modified to account for varied entry times and IPT-weighted for confounding control. Early cases that occurred when the risk set was smaller than 50 were postponed to avoid artificially large jumps in cumulative incidence at early gestational ages.

CHAPTER 6: ONDANSETRON USE IN EARLY PREGNANCY AND THE RISK OF LATE PREGNANCY OUTCOMES

6.1 Introduction

With increasing use in the United States, the safety of ondansetron use in pregnancy for nausea and vomiting is a topic of interest (3). Ondansetron, a 5-HT_3-receptor antagonist, is approved by the Food and Drug Administration (FDA) for treating chemotherapy-induced 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 (27). However, more than 20% of pregnant women were estimated to have filled a prescription for ondansetron in the US in 2014 -- a dramatic increase in use since becoming available in generic form in 2007 (3). 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 (4,6–8,36). Less attention has been paid to other outcomes, including common but less serious adverse pregnancy outcomes such as preterm birth and hypertensive disorders, or rare and serious outcomes including stillbirth. As nausea and vomiting are symptoms experienced by nearly 80% of women during early pregnancy (1), modest effects on common outcomes could result in adverse outcomes for large numbers of pregnant women every year.

Studies evaluating adverse outcomes other than birth defects in association with ondansetron use have compared women using ondansetron to a general population of pregnant women not using ondansetron (5,10). 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 (55). Additionally, this comparison helps inform treatment decisions for women requiring symptoms relief.

Therefore, the objective of this study was to estimate the effect of ondansetron use on stillbirth, preterm birth, birth weight, and hypertensive disorders compared to use of alternative antiemetic medications commonly used in pregnancy in the U.S., promethazine and metoclopramide.

6.2 Methods

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.

Identifying pregnancies

Pregnancies were defined in a prospective fashion 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 Appendix Table D.1), or the initiation of a pregnancy event in the Epic EHR system. Pregnancies were followed forward from this index date until evidence of 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.

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 (27). These drugs have historically been widely used during pregnancy in the US (3,70), however recently have decreased in use due to the availability of ondansetron in generic form and its more favorable side effect profile (3,29). 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, and administered prescriptions included all medications taken by the patient in a health care facility, including intravenous medications. 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.

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 10^{th} percentile of birth weights by gestational week of birth using the birth weight distribution for the U.S. in the year 2000 (82). The most appropriate method for studying low birth weight as an adverse pregnancy outcome is controversial (83,84), therefore differences in the birth weight distribution among term live births was 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 (85,86).

All diagnosis codes used to define outcomes are listed in Appendix Table C.1.

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 or other Pacific Islander. 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. Pre-pregnancy 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.

Statistical analysis

To estimate the association between antiemetic use and outcomes, risk ratios (RRs) were estimated using survival analysis methods. The cumulative incidences of stillbirth, preterm birth, small for gestational age status, and gestational hypertensive disorders were estimated separately in each antiemetic group using a modified Fine and Gray estimator that accounts for competing events and varied entry times (60,61). 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 6.1. 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 (58).

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.

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 (71). Measured confounding was controlled using stabilized inverse probability of treatment weights (76). 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 (74). We used 1000 nonparametric bootstrapped samples with replacement (63) and report empirical 95% confidence intervals estimated by the 2.5th and 97.5th percentiles of the distribution.

Due to the small number of cases of stillbirth, bootstrap methods for estimating confidence intervals for RRs were unstable. Therefore, logistic regression was used to estimate an odds ratio (OR) for stillbirth in the ondansetron group versus alternative antiemetics with all completed pregnancies (excluding those lost to follow-up) in the denominator. We interpreted the OR as approximating the RR because the outcome of stillbirth is rare (58).

Analyses were completed in R version 3.5.3 using the mice, mstate, and boot packages (77–80).

Per-protocol analysis

Women may receive prescriptions for different antiemetics if their first prescription does not achieve symptom control; this will result in 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 (65).

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 intravenous 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 survived until the start of 21st week to avoid inclusion of immortal time between the first eligible antiemetic order and the first prenatal care visit (87). 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 (58). 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 6.1.

6.3 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 6.2). Loss to follow-up was similar in both groups, accounting for 29% of ondansetron-exposed women and 36% of comparator-exposed women.

Few differences were observed in patient characteristics between antiemetic exposure groups (Table 6.1). 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 (IQR): 50-86) in the ondansetron group and 67 days (IQR: 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 included in the propensity score with absolute standardized mean differences less than 10% (75).

Main results

Results from the intent-to-treat style analysis are presented in Table 6.2. The risk of stillbirth was 0.8% in the ondansetron group and 0.4% in the comparator group (crude OR=1.95, 95% CI 0.55, 6.93). After weighting, no association between stillbirth and ondansetron was apparent (OR=1.32, 95% CI 0.39, 4.53). The risk of preterm birth was 8.5% in the ondansetron group and 9.6% in the comparator group. The weighted RR indicated no association between antiemetic use and preterm birth (RR 0.91, 95% CI 0.40, 2.54), or early preterm birth before 34 weeks (RR 0.75, 95% CI 0.22, 4.52). Risk of SGA was also similar between antiemetic groups (8.0% in the ondansetron group, 6.1% in the comparator group; weighted RR 1.19, 95% 0.52, 3.38). 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 (RR 0.90,95% CI 0.47, 1.89).

Per-protocol analysis and other sensitivity analyses

Results of the sensitivity analyses are presented in Figure 6.3. 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; follow-up was censored at the gestational age of this second antiemetic prescription in the per-protocol analysis, which included 1,722 ondansetron and 921 comparator exposed women. 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 Appendix Table C.2), 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 very consistent for preterm birth, but

showed more variability for other outcomes. Overall, the plots show wide confidence intervals and do not provide strong evidence of differences in risk between antiemetic groups. Sensitivity analyses were not completed for stillbirth due to the small number of cases.

Birth weight distribution

Results from linear regression analyses comparing birth weight distributions among term live births are presented in Table 6.3. No difference in mean birth weight was observed in the main analysis of in the per-protocol and prenatal care sensitivity analyses. In the administered analysis, mean birth weight was 81 grams lower in the ondansetron group.

6.4 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 stillbirth, preterm birth, hypertensive disorders, or birth weight outcomes. 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 SGA may be suggestive of an increased risk among ondansetron users, however 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 no longer observed after covariate weighting.

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 RRs 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.

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 (24), however recent studies have suggested these associations can be attributed to maternal characteristics (88,89). 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 (5). Ondansetron exposed births in western Australia had higher risk of preterm birth, preeclampsia, and low birth weight compared to non-users (10); 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 (5,10).

We analyzed women starting at the gestational age of their first eligible antiemetic prescription and accounted for all events occurring after 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. Conditional analyses assume there are no competing events and are subject to bias if competing events differ between exposure groups (58,90). In perinatal pharmacoepidemiology, we are interested in intervening at the point of drug use in pregnancy. Therefore, unconditional risk contrasts are the most appropriate to answer the question of what would have happened had women been exposed to an alternative therapy (or no therapy, if appropriate).

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 (91). 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 (85,86). 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.

In summary, we did not observe strong evidence of a difference in risk of stillbirth, preterm birth, hypertensive disorders, or birth weight outcomes between ondansetron users and comparator antiemetic users. Our findings, based on a rigorous active comparator analysis

reducing confounding by design, adds to the body of literature assessing the safety of ondansetron use during pregnancy.

Table 6.1. Characteristics of pregnant women seen at UNC Health Care between 2014-2017 with antiemetic exposure by antiemetic exposure status

	Unweighted			IPT-Weighted, trimmed
	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, N (%)				
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, N (%)				
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, N (%)	263 (15.1)	127 (13.6)	0.04	0.01
Missing	33 (1.9)	17 (1.8)		
Smoking status, N (%)				
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, N (%)				
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 BMI, N (%)				
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, N (%)				
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

	Unweighted			IPT-Weighted, trimmed
	Ondansetron (N=1742)	**Comparators (N=935)**	**Absolute standardized difference**	**Absolute standardized difference**
Concomitant medications, N (%), continued				
NSAIDs	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
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 (1 or more visits before antiemetic order), N (%)				
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, N (%)				
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, N (%)				
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, N (%)				
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
Care setting of antiemetic order, N (%)				
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, N (%)				
Inpatient administration	745 (42.8)	442 (47.3)	0.09	0.04
Intravenous administration	443 (25.4)	380 (40.6)	0.33	0.04
Orders for other antiemetics[1], N (%)	238 (13.7)	267 (28.6)	0.37	0.04

	Unweighted			IPT-Weighted, trimmed
	Ondansetron (N=1742)	**Comparators (N=935)**	**Absolute standardized difference**	**Absolute standardized difference**
Indications for antiemetics, N (%)				
Nausea and vomiting	565 (32.4)	374 (40.0)	0.16	0.03
HEG (inpatient)	23 (1.3)	15 (1.6)	0.02	0.01
HEG (emergency)	285 (16.4)	181 (19.4)	0.08	0.03

Table 6.2. Risk of late pregnancy outcomes among pregnant women seen at UNC Health Care between 2014-2017 with ondansetron or comparator antiemetic exposure, conditional on survival until week 21

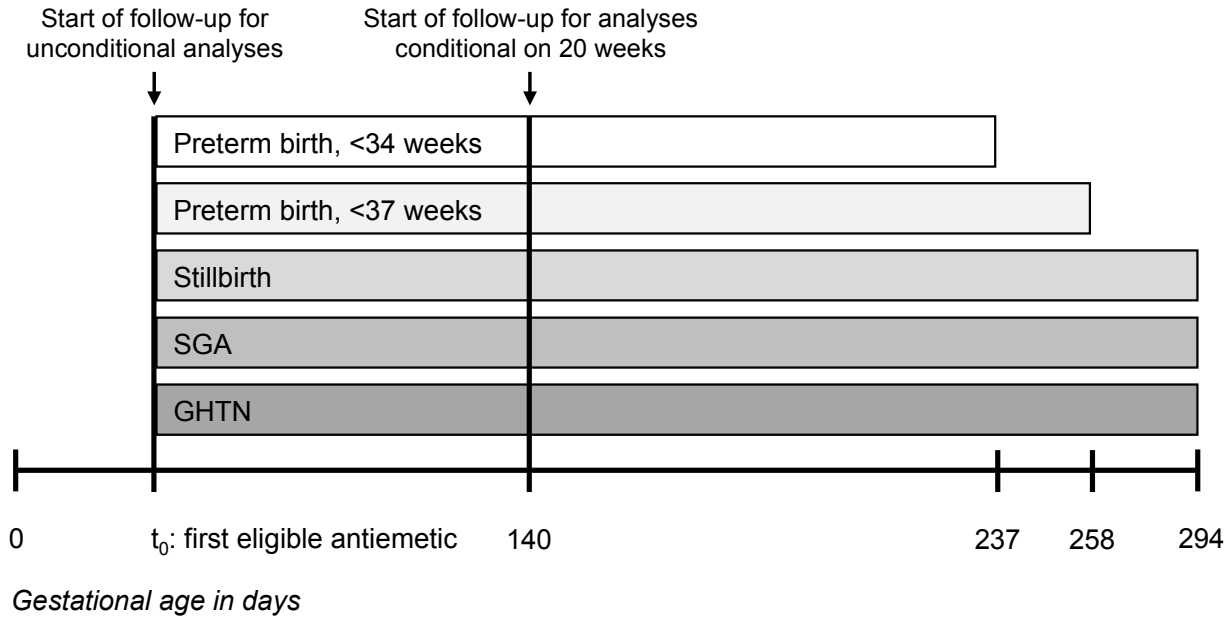
	N cases / N total	Unweighted cumulative incidence[1] (%) (95% CI)	Unweighted RR (95% CI)	Weighted, trimmed RR (95% CI)
Stillbirth				
Ondansetron	12 / 1742	0.8% (0.1, 2.2)	1.95 (0.55, 6.93)[2]	1.32 (0.39, 4.53)[2]
Comparators	3 / 935	0.4% (0, 1.5)	1	1
Preterm birth, <37 weeks				
Ondansetron	125 / 1742	8.5% (5, 12.8)	0.89 (0.42, 2.11)	0.91 (0.40, 2.54)
Comparators	67 / 935	9.6% (4.8, 16.5)	1	1
Preterm birth, <34 weeks				
Ondansetron	35 / 1742	2.3% (0.9, 4.7)	0.74 (0.23, 3.46)	0.75 (0.22, 4.52)
Comparators	22 / 935	3.1% (0.8, 7.4)	1	1
Hypertensive disorders				
Ondansetron	177 / 1742	12.6% (8.0, 17.7)	0.79 (0.43, 1.47)	0.90 (0.47, 1.89)
Comparators	107 / 935	15.9% (9.4, 24.0)	1	1
Small for gestational age				
Ondansetron	148 / 1742	8.0% (4.8, 12.1)	1.33 (0.63, 3.34)	1.19 (0.52, 3.38)
Comparators	64 / 935	6.1% (2.6, 10.5)	1	1

[1]Estimated using the Fine and Gray method accounting for varied entry times (61)

Table 6.3. Analysis of mean birth weight difference between antiemetic groups among term live births

	N	Mean birth weight in grams (SD)	Crude difference in means (95% CI)	Weighted difference in means (95% CI)	Additional adjustment for gestational age (95% CI)
Main analysis					
Ondansetron	1117	3353 (481)	38.3 (-13.4, 90.0)	5.9 (-48.5, 60.3)	13.8 (-58.9, 86.5)
Comparators	541	3315 (451)	0	0	0
Per-protocol					
Ondansetron	934	3355 (470)	37.6 (-19.4, 94.7)	0.4 (-65.4, 66.3)	2.1 (-59.9, 63.9)
Comparators	423	3317 (449)	0	0	0
Administered					
Ondansetron	399	3294 (472)	-11.2 (-90.9, 68.4)	-55.9 (-143, 32.0)	-80.9 (-166.5, 4.6)
Comparators	243	3305 (450)	0	0	0
Prenatal care					
Ondansetron	779	3373 (491)	75.3 (6.0, 144.7)	4.3 (-72.3, 81.0)	7.4 (-44.1, 58.9)
Comparators	303	3298 (455)	0	0	0

Figure 6.1. Period of cumulative incidence estimation for all outcomes



Legend: 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 20 weeks, or 140 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.

Figure 6.2. Inclusion and exclusion of pregnancies in the analysis

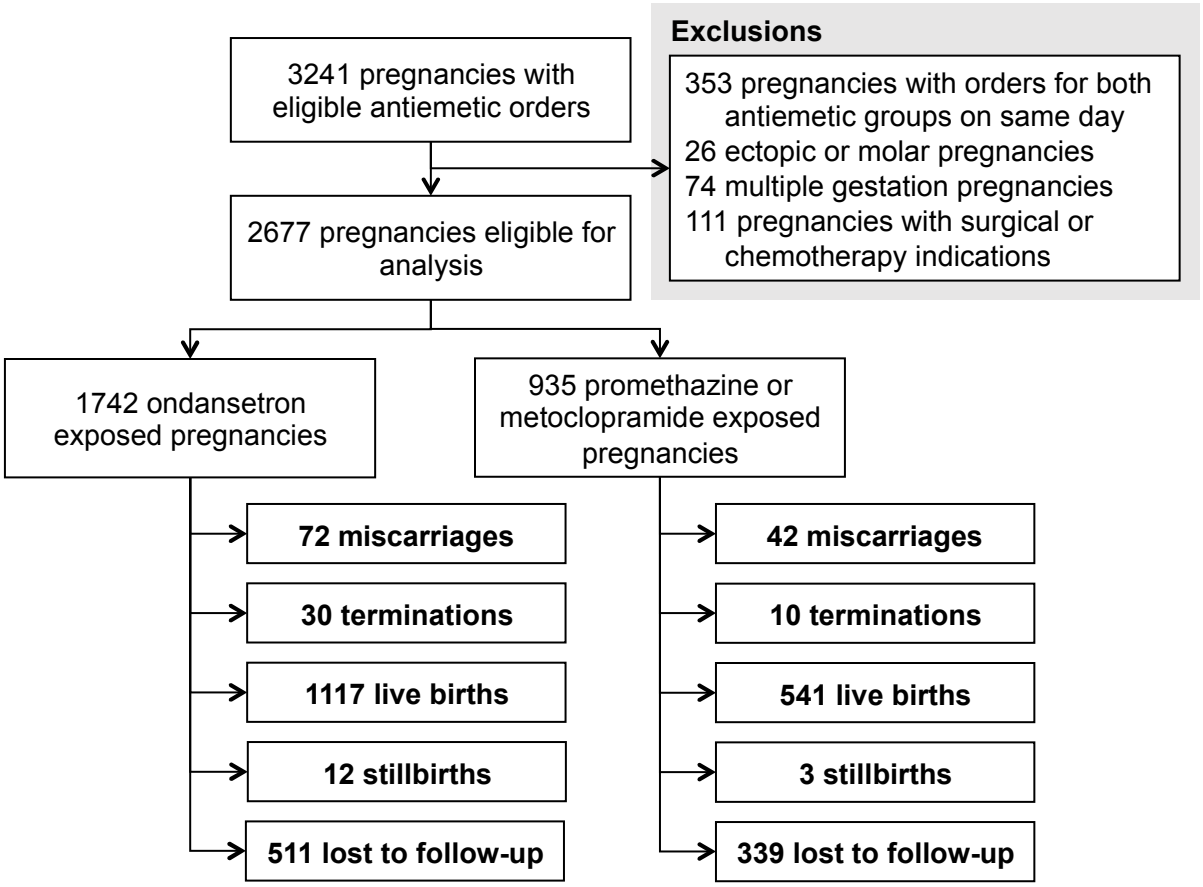
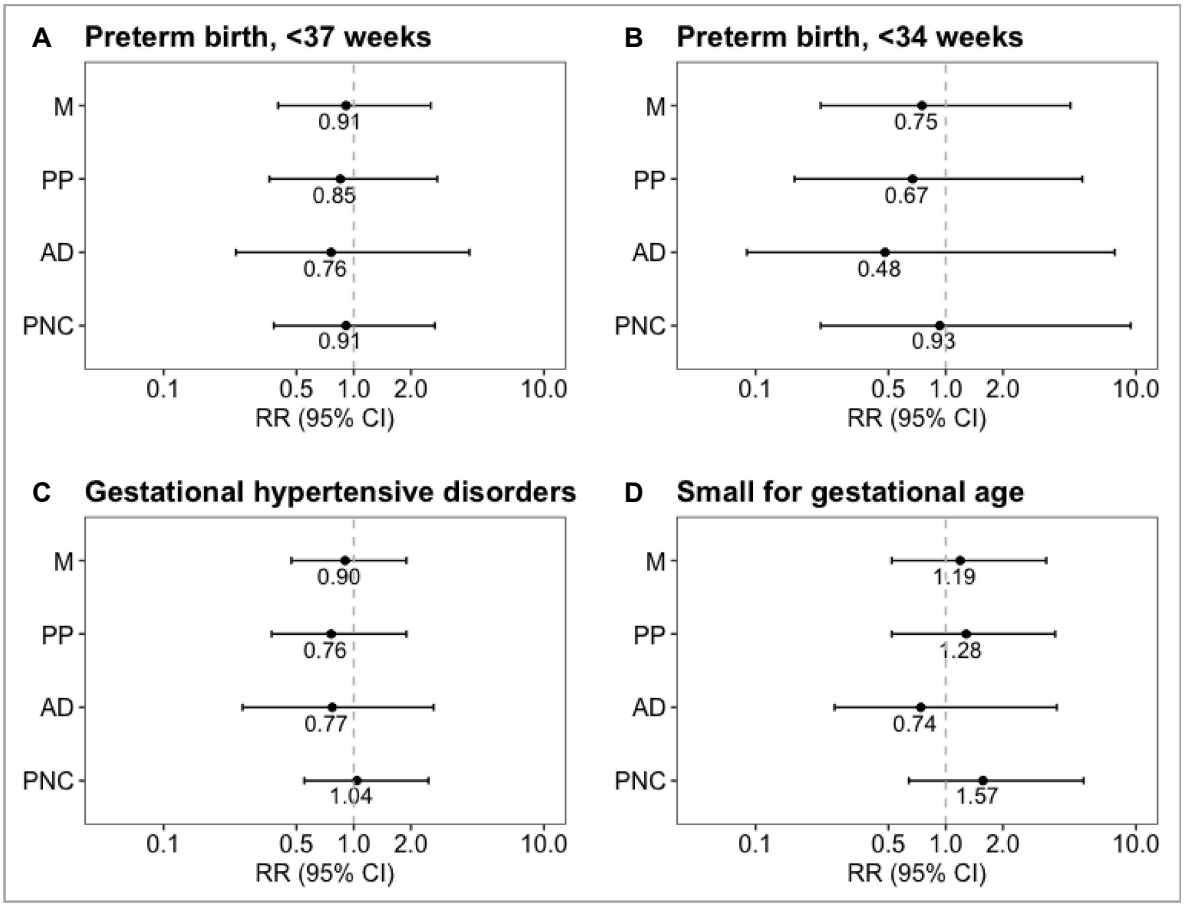


Figure 6.3. Association of late pregnancy outcomes among pregnant women seen at UNC Health Care between 2014-2017 with ondansetron or comparator antiemetic exposure in per-protocol and sensitivity analyses



Legend: Risk ratios and 95% confidence intervals for the results of the main analysis (M) and sensitivity analyses (PP: per-protocol analysis; AD: administered analysis; PNC: prenatal care analysis) for (A) and (B) preterm birth, (C) gestational hypertensive disorders, and (D) small for gestational age.

CHAPTER 7: DISCUSSION

7.1 Summary of findings

The objective of Aim 1 was to estimate the effect of ondansetron use during pregnancy for treatment of nausea and vomiting on miscarriage when compared to use of alternative antiemetics of promethazine and metoclopramide. We did not observe a difference in risk of miscarriage between the ondansetron group and the comparator group. This result was maintained in sensitivity analyses that were designed to limit the impact of exposure misclassification. The per-protocol analysis, which censored women at the gestational age of receiving a prescription from the other antiemetic group, resulted in similarly null findings. Restricting exposure to antiemetics administered in a healthcare facility supported the main null result. We further considered a latency period for miscarriage and assumed that miscarriage was clinically recognized 23 days after pregnancy failure was in progress. This analysis also did not suggest an increased risk of miscarriage with ondansetron use compared to comparator antiemetic use, however small numbers of cases did not allow for strong conclusions.

The objective of Aim 2 was to estimate the effects of ondansetron use in early pregnancy on a series of adverse pregnancy outcomes that occur in late pregnancy, after 20 weeks. We observed no meaningful differences in risk of stillbirth, preterm birth, hypertensive disorders, or birth weight outcomes. The risk of early preterm birth, defined by live birth at less than 34 weeks, was lower in the ondansetron group, but small numbers of cases resulted in wide confidence intervals. Sensitivity analyses that explored the potential for exposure misclassification and restricted to a population with prenatal care did not change our conclusions.

7.2 Public health implications

Results from studies of the safety of ondansetron use during pregnancy are most likely to impact treatment decisions for women with mild or moderate NVP. While HEG and severe NVP nearly always require treatment, the decision to offer prescription antiemetics to women with mild or moderate NVP can change based on the medications available, the cost of those medications, and the known or perceived safety of those medications. A woman with mild or moderate symptoms and her provider will weigh the benefits of symptom control with the risks to her and her infant.

The benefits to symptom control can be inferred from studies of women experiencing NVP. A cohort of 713 women with NVP in Norway was surveyed about their symptom severity, quality of life, and desire to have more children (92). Among women pregnant at the time of the survey, NVP severity was associated with reduced quality of life. Most of the women (70%) reported that NVP interfered with their ability to manage a household or maintain social interactions. Similar proportions also noted difficulty in caring for children. More than half reported taking sick leave from work. Women with severe symptoms considered not getting pregnant again (75%) and whether to terminate the NVP-affected pregnancy (27%). The impact of NVP in mild or moderate cases on psychosocial wellbeing was specifically investigated in a survey of Canadian and American women calling a hotline for NVP concerns (93). More than half of the women with mild or moderate symptoms reported feelings of depression some or all of the time. A review of studies evaluating the effect of NVP on multiple facets of life for affected women reported similar trends across the literature (94).

In addition to the quality of life and wellbeing of affected women, there are economic benefits of symptom control. Women often miss work and sometimes require their partner to miss work as well (92,95). Utilization of caregivers may be required for children. Women who delay seeking treatment because they believe NVP is a normal part of pregnancy may end up with additional expenses if symptoms progress and emergency care is required (20).

Ondansetron has been shown to be effective at symptom control for all nausea and vomiting symptom severities (28). Ondansetron users report fewer side effects than metoclopramide users (29). Ondansetron does not have the common side effect of drowsiness shared by metoclopramide, promethazine, doxylamine/pyridoxine, and other antihistamines. Therefore, ondansetron may offer an effective treatment option for women who require symptom control without loss of productivity and quality of life due to drowsiness. If the safety of ondansetron is supported in future studies, more women may be able to benefit from nausea and vomiting symptom control and maintain their daily routines during pregnancy.

7.3 Future research

The current study improved on previous research in numerous ways. Use of an active comparator comprised of women receiving prescriptions for metoclopramide and promethazine reduced the potential of confounding by NVP severity by comparing ondansetron users to a population of similarly treated women. Prospective definition of pregnancies within the EHR database allowed for studying all pregnancies rather than all live births, allowing for the study of miscarriage and stillbirth as key outcomes. Assembling a cohort of all pregnancies also allowed for consideration of pregnancies lost to follow-up, which may still contribute key outcomes that occur before delivery. Advanced survival analysis methods were used to account for the varied gestational age at first antiemetic prescription and the impact of competing events. Future research should build on the methodological improvements of the current research by addressing the main limitations: (1) small sample sizes, (2) potential misclassification of antiemetic exposure status, and (3) possible missing data due to receiving care outside of the single health care system included.

Use of EHR data linked to insurance claims would address many of the noted limitations. Using linked data would combine the availability of gestational age and delivery records in EHR with records of prescription fills and care received at multiple institutions from claims data. Insurance claims data includes information on prescription fills rather than prescription orders,

therefore limiting exposure misclassification due to antiemetic prescriptions that are never filled. Insurance claims data also includes information on all care received and reimbursed through the insurance plan, regardless of health care system where the care was received. This allows for inclusion of prescriptions filled based on care received outside of the included EHR system, in addition to observing pregnancy outcomes for some women who are lost to follow-up in the EHR system.

Use of prescription fills from insurance claims data likely decreases exposure misclassification but does not eliminate it; women might fill prescriptions for antiemetics and never take them or take them rarely. While prospective patient self-report of antiemetic use is the gold standard for exposure classification, this strategy is resource intensive and difficult to achieve for large sample sizes. Studies that utilize EHR systems could integrate research questions in the EHR and have providers ask about antiemetic use during prenatal care visits. This strategy may result in missing data due to lack of participation or lack of follow-up in women little to no prenatal care, however results could be used to inform quantitative bias analyses for exposure misclassification.

7.4 Conclusions

In summary, we did not observe evidence of a difference in risk of miscarriage, preterm birth, hypertensive disorders, or birth weight outcomes between ondansetron users and comparator antiemetic users. These findings are based on advanced survival analysis methods that appropriately account for the gestational age of antiemetic use and competing events along the pregnancy timeline, and a rigorous active comparator analysis that reduces confounding by design. This work addresses a clinically relevant question about whether ondansetron is as safe as other commonly utilized antiemetic options, and therefore adds to the body of evidence that physicians and women can use when assessing the need and desire for treatment of nausea and vomiting symptoms during early pregnancy.

APPENDIX A. SUPPLEMENTAL METHODS FOR DEFINING THE PREGNANCY COHORT

A.1 Defining pregnancies based on pregnancy and delivery episodes

Data from pregnancy and delivery episodes were assumed to be accurate and used as the primary method for defining pregnancies. Pregnancy episode records were cleaned to format the EDD and reconcile overlapping episodes for the same woman. Pregnancy episodes for one woman were considered overlapping if the pregnancy period (the time from pregnancy start to EDD) overlapped. To remedy duplicate and overlapping pregnancy episodes, the following steps were taken. If two episodes had EDDs that were less than 60 days apart, the episodes were treated as duplicates and the episode that was started later was assumed to be accurate. Overlapping episodes with EDDs greater than 60 days apart were retained as separate episodes to allow for the possibility that the first pregnancy ended before the EDD (miscarriage, termination, premature delivery) and the actual pregnancies did not overlap. Finally, pregnancy episodes without delivery dates were deleted if the episode overlapped with an earlier pregnancy episode and estimated start of pregnancy was earlier than previous pregnancy outcome, assuming these entries were made in error.

Delivery data was linked to episode data based on medical record numbers for the mother and dates and was cleaned to contain one record per pregnancy rather than one record per infant (in the case of multiple pregnancies). Pregnancy outcome date, pregnancy outcome type, and gestational age were formatted and retained. Errors in linkages were manually corrected (i.e. episode and delivery did not link but contained corresponding information). Unrealistic gestational ages or delivery dates were corrected by using other information in the record (i.e. gestational age recalculated using delivery date and EDD, or delivery date recalculated using gestational age and EDD). If the delivery date was missing, the infant admission date was used instead. Records that were missing both a delivery date and an EDD were deleted because they contained no useful information for defining pregnancies.

A.2 Defining pregnancies based on linked diagnosis and procedure codes

When delivery episode data was not available, diagnosis and procedure codes were used to define pregnancy outcomes. Diagnosis and procedure codes were linked to pregnancy episode data for approximately 30% of pregnancy episodes. Diagnosis and procedure codes were also used to identify pregnancy outcomes for women without pregnancy episode data. The algorithm used the same rules to classify outcomes using diagnosis and procedure codes in cases where pregnancy episodes were available and not available, therefore the methods are described once in this section. The codes used for defining pregnancy outcomes are listed in Appendix Tables D.3-D.8.

The pregnancy outcome date was chosen by prioritizing procedure codes over diagnosis codes. The first date of a procedure code was chosen as the outcome date; if no procedure codes were linked, the first date of a diagnosis code was chosen as the outcome date.

After the pregnancy outcome date was chosen, all diagnosis and procedure codes within 5 days before and 5 days after that date were retained. The pregnancy outcome type was classified based on these codes using the following hierarchy when discrepant codes were found:

1. Miscarriage
2. Stillbirth
3. Termination
4. Live birth and stillbirth (for multiple pregnancies)
5. Live birth
6. Ectopic and molar pregnancies
7. Abortion of unknown type (classified as miscarriage)
8. Delivery of unknown type (classified as live birth)

Code lists for each of these pregnancy outcome types are listed in Appendix Tables D.3-D.8.

This hierarchy of pregnancy outcome types was chosen because miscarriage and stillbirth are key study outcomes. All potential miscarriage and stillbirth cases were captured in this algorithm and were verified through medical record review. The last two outcome categories noted in the hierarchy (7 and 8) were special scenarios where the codes were not specific to the type of delivery or abortion. Therefore, if an unspecified delivery procedure code was found in the record (without other classifiers), the delivery was classified as a live birth. If an unspecified abortion code was found in the record (without other classifiers), the delivery was classified as a miscarriage.

APPENDIX B: SUPPLEMENTAL MATERIALS FOR AIM 1

Table B.1. Risk of miscarriage at 140 days with no adjustment of early event times

			RD (95% CI) (%)		RR (95% CI)	
	N cases / N total	Unweighted cumulative incidence (%)[1] (95% CI)	Unweighted	Weighted, trimmed	Unweighted	Weighted, trimmed
Main analysis						
Ondansetron	64 / 1712	13.3% (4.9, 32.1)	4.5% (-11.8, 25.4)	2.9% (-25.4, 24.1)	1.51 (0.37, 6.8)	1.31 (0.23, 8.51)
Comparators	31 / 908	8.8% (2.7, 21.8)	0	0	1	1
Per-protocol						
Ondansetron	64 / 1708	14.0% (5.3, 33.9)	6.0% (-9.3, 28.2)	3.6% (-24.7, 26.5)	1.76 (0.46, 7.95)	1.39 (0.25, 9.85)
Comparators	30 / 903	7.9% (2.3, 20.6)	0	0	1	1
Administered						
Ondansetron	39 / 720	17.9% (5.5, 48.9)	8.3% (-21.0, 41.7)	3.3% (-30.6, 39.6)	1.86 (0.30, 15.61)	1.28 (0.21, 16.9)
Comparators	13 / 424	9.6% (1.3, 34.9)	0	0	1	1
23-day latency						
Ondansetron	27 / 1463	33.7% (3.0, 94.6)	3.9% (-82.5, 82.9)	-39.8% (-89.8, 88.4)	1.13 (0.07, 35.24)	0.31 (0.05, 74.28)
Comparators	14 / 758	29.8% (1.2, 100.0)	0	0	1	1
All LTFU as miscarriage cases						
Ondansetron	279 / 1712	32.0% (21.6, 49.7)	-5.9 (-49.1, 20.5)	4.6 (-37.0, 26.6)	0.85 (0.38, 1.79)	1.17 (0.43, 2.36)
Comparators	170 / 908	37.8% (21, 78.3)	0	0	1	1
All LTFU as non-cases						
Ondansetron	64 / 1712	13.0% (4.7, 31.8)	4.6 (-11.4, 25.0)	2.8 (-25.1, 23.8)	1.54 (0.38, 7.11)	1.31 (0.23, 8.57)
Comparators	31 / 908	8.4% (2.5, 21.4)	0	0	1	1

[1]Estimated using the Fine and Gray method accounting for varied entry times (61)

APPENDIX C: SUPPLEMENTAL MATERIALS FOR AIM 2

Table C.1. Diagnosis codes used to define study outcomes

Code	Code type	Description
Gestational hypertensive disorders		
642.3x	ICD-9 diagnosis	Transient hypertension of pregnancy
642.4x	ICD-9 diagnosis	Mild or unspecified pre-eclampsia
642.5x	ICD-9 diagnosis	Severe pre-eclampsia
642.6x	ICD-9 diagnosis	Eclampsia
642.7x	ICD-9 diagnosis	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension
O11.x	ICD-10 diagnosis	Pre-existing hypertension with pre-eclampsia
O13.x	ICD-10 diagnosis	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14.0x	ICD-10 diagnosis	Mild to moderate pre-eclampsia
O14.1x	ICD-10 diagnosis	Severe pre-eclampsia
O14.2x	ICD-10 diagnosis	HELLP syndrome (HELLP)
O14.9x	ICD-10 diagnosis	Unspecified pre-eclampsia
O15.0x	ICD-10 diagnosis	Eclampsia complicating pregnancy
Stillbirth		
656.40-656.43	ICD-9 diagnosis	Intrauterine death, affecting management of mother
768.0-768.1	ICD-9 diagnosis	Fetal death from asphyxia or anoxia
V27.1	ICD-9 diagnosis	Outcome of delivery, single stillborn
V27.4	ICD-9 diagnosis	Outcome of delivery, twins, both stillborn
V27.7	ICD-9 diagnosis	Outcome of delivery, other multiple birth, all stillborn
O36.4XX0-O36.4XX9	ICD-10 diagnosis	Maternal care for intrauterine death
Z37.1	ICD-10 diagnosis	Single stillbirth
Z37.4	ICD-10 diagnosis	Twins, both stillborn
Z37.7	ICD-10 diagnosis	Other multiple births, all stillborn
P95	ICD-10 diagnosis	Stillbirth

Table C.2. Risk of late pregnancy outcomes among pregnant women seen at UNC Health Care between 2014-2017 with ondansetron or comparator antiemetic exposure, conditional on survival until the start of gestational week 21

	N cases / N total	Unweighted cumulative incidence[1] (95% CI)	Unweighted RR (95% CI)	Weighted, trimmed (95% CI)
Preterm birth, <37 weeks				
Ondansetron	125 / 1403	10.4 (8.7, 12.1)	0.92 (0.69, 1.24)	0.89 (0.40, 2.21)
Comparators	67 / 729	11.3 (8.7, 14.1)	1	1
Preterm birth, <34 weeks				
Ondansetron	35 / 1403	2.8 (1.9, 3.7)	0.79 (0.49, 1.41)	0.81 (0.20, 4.86)
Comparators	22 / 729	3.5 (2.1, 4.9)	1	1
Hypertensive disorders				
Ondansetron	177 / 1403	15.3 (13.4, 17.4)	0.81 (0.65, 1.01)	0.86 (0.48, 1.66)
Comparators	107 / 729	19.0 (15.8, 22.2)	1	1
Small for gestational age				
Ondansetron	148 / 1403	10.7 (8.9, 12.3)	1.21 (0.92, 1.65)	1.25 (0.52, 3.09)
Comparators	64 / 729	8.8 (6.7, 10.9)	1	1

[1]Estimated using the Fine and Gray method accounting for competing events

APPENDIX D: DIAGNOSIS AND PROCEDURE CODES TO DEFINE COHORT, OUTCOMES, AND COVARIATES

Table D.1: Diagnosis and procedure codes used to identify early pregnancy

Code	Code Type	Description
10904ZU	ICD-10-PCS	Amniocentesis
59000	CPT	Amniocentesis, any method
59001	CPT	Abdominal aspiration
59070	CPT	Transabdominal amnioinfusion, including ultrasound guidance
59072	CPT	Fetal umbilical cord occlusion, including ultrasound guidance
59074	CPT	Fetal fluid drainage, including ultrasound guidance
59076	CPT	Fetal shunt placement, including ultrasound guidance
59320	CPT	Cervical cerclage
59897	CPT	Fetal invasive procedure
640.03	ICD-9 dx	Threatened abortion, antepartum condition or complication
640.83	ICD-9 dx	Other specified hemorrhage in early pregnancy, antepartum condition or complication
640.93	ICD-9 dx	Unspecified hemorrhage in early pregnancy, antepartum condition or complication
641.03	ICD-9 dx	Placenta previa without hemorrhage, antepartum condition or complication
641.13	ICD-9 dx	Hemorrhage from placenta previa, antepartum condition or complication
641.23	ICD-9 dx	Premature separation of placenta, antepartum condition or complication
641.33	ICD-9 dx	Antepartum hemorrhage associated with coagulation defects, antepartum condition or complication
641.83	ICD-9 dx	Other antepartum hemorrhage, antepartum condition or complication
641.93	ICD-9 dx	Unspecified antepartum hemorrhage, antepartum condition or complication
642.03	ICD-9 dx	Benign essential hypertension complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication
642.13	ICD-9 dx	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication
642.23	ICD-9 dx	Other pre-existing hypertension, complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication
642.33	ICD-9 dx	Transient hypertension of pregnancy, antepartum condition or complication
642.43	ICD-9 dx	Mild or unspecified pre-eclampsia, antepartum condition or complication
642.53	ICD-9 dx	Severe pre-eclampsia, antepartum condition or complication
642.63	ICD-9 dx	Eclampsia, antepartum condition or complication
642.73	ICD-9 dx	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, antepartum condition or complication
642.93	ICD-9 dx	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
643.03	ICD-9 dx	Mild hyperemesis gravidarum, antepartum condition or complication
643.13	ICD-9 dx	Hyperemesis gravidarum with metabolic disturbance, antepartum condition or complication
643.23	ICD-9 dx	Late vomiting of pregnancy, antepartum condition or complication

Code	Code Type	Description
643.83	ICD-9 dx	Other vomiting complicating pregnancy, antepartum condition or complication
643.93	ICD-9 dx	Unspecified vomiting of pregnancy, antepartum condition or complication
644.03	ICD-9 dx	Threatened premature labor, antepartum condition or complication
644.13	ICD-9 dx	Other threatened labor, antepartum condition or complication
646.03	ICD-9 dx	Papyraceous fetus, antepartum condition or complication
646.13	ICD-9 dx	Edema or excessive weight gain in pregnancy, without mention of hypertension, antepartum condition or complication
646.23	ICD-9 dx	Unspecified renal disease in pregnancy, without mention of hypertension, antepartum condition or complication
646.33	ICD-9 dx	Recurrent pregnancy loss, antepartum condition or complication
646.43	ICD-9 dx	Peripheral neuritis in pregnancy, antepartum condition or complication
646.53	ICD-9 dx	Asymptomatic bacteriuria in pregnancy, antepartum condition or complication
646.63	ICD-9 dx	Infections of genitourinary tract in pregnancy, antepartum condition or complication
646.73	ICD-9 dx	Liver and biliary tract disorders in pregnancy, antepartum condition or complication
646.83	ICD-9 dx	Other specified complications of pregnancy, antepartum condition or complication
646.93	ICD-9 dx	Unspecified complication of pregnancy, antepartum condition or complication
647.03	ICD-9 dx	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
647.13	ICD-9 dx	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
647.23	ICD-9 dx	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
647.33	ICD-9 dx	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
647.43	ICD-9 dx	Malaria in the mother, antepartum condition or complication
647.53	ICD-9 dx	Rubella in the mother, antepartum condition or complication
647.63	ICD-9 dx	Other viral diseases in the mother, antepartum condition or complication
647.83	ICD-9 dx	Other specified infectious and parasitic diseases of mother, antepartum condition or complication
647.93	ICD-9 dx	Unspecified infection or infestation of mother, antepartum condition or complication
648.03	ICD-9 dx	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
648.13	ICD-9 dx	Thyroid dysfunction of mother, antepartum condition or complication
648.23	ICD-9 dx	Anemia of mother, antepartum condition or complication
648.33	ICD-9 dx	Drug dependence of mother, antepartum condition or complication
648.43	ICD-9 dx	Mental disorders of mother, antepartum condition or complication
648.53	ICD-9 dx	Congenital cardiovascular disorders of mother, antepartum condition or complication
648.63	ICD-9 dx	Other cardiovascular diseases of mother, antepartum condition or complication

Code	Code Type	Description
648.73	ICD-9 dx	Bone and joint disorders of back, pelvis, and lower limbs of mother, antepartum condition or complication
648.83	ICD-9 dx	Abnormal glucose tolerance of mother, antepartum condition or complication
648.93	ICD-9 dx	Other current conditions classifiable elsewhere of mother, antepartum condition or complication
649.03	ICD-9 dx	Tobacco use disorder complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
649.13	ICD-9 dx	Obesity complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
649.23	ICD-9 dx	Bariatric surgery status complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
649.33	ICD-9 dx	Coagulation defects complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
649.43	ICD-9 dx	Epilepsy complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
649.53	ICD-9 dx	Spotting complicating pregnancy, antepartum condition or complication
649.63	ICD-9 dx	Uterine size date discrepancy, antepartum condition or complication
649.73	ICD-9 dx	Cervical shortening, antepartum condition or complication
651.03	ICD-9 dx	Twin pregnancy, antepartum condition or complication
651.13	ICD-9 dx	Triplet pregnancy, antepartum condition or complication
651.23	ICD-9 dx	Quadruplet pregnancy, antepartum condition or complication
651.83	ICD-9 dx	Other specified multiple gestation, antepartum condition or complication
651.93	ICD-9 dx	Unspecified multiple gestation, antepartum condition or complication
654.03	ICD-9 dx	Congenital abnormalities of uterus, antepartum condition or complication
654.13	ICD-9 dx	Tumors of body of uterus, antepartum condition or complication
654.23	ICD-9 dx	Previous cesarean delivery, antepartum condition or complication
654.33	ICD-9 dx	Retroverted and incarcerated gravid uterus, antepartum condition or complication
654.43	ICD-9 dx	Other abnormalities in shape or position of gravid uterus and of neighboring structures, antepartum condition or complication
654.53	ICD-9 dx	Cervical incompetence, antepartum condition or complication
654.63	ICD-9 dx	Other congenital or acquired abnormality of cervix, antepartum condition or complication
654.73	ICD-9 dx	Congenital or acquired abnormality of vagina, antepartum condition or complication
654.83	ICD-9 dx	Congenital or acquired abnormality of vulva, antepartum condition or complication
654.93	ICD-9 dx	Other and unspecified abnormality of organs and soft tissues of pelvis, antepartum condition or complication
655.03	ICD-9 dx	Central nervous system malformation in fetus, antepartum condition or complication
655.13	ICD-9 dx	Chromosomal abnormality in fetus, affecting management of mother, antepartum condition or complication
655.23	ICD-9 dx	Hereditary disease in family possibly affecting fetus, affecting management of mother, antepartum condition or complication
655.33	ICD-9 dx	Suspected damage to fetus from viral disease in the mother, affecting management of mother, antepartum condition or complication

Code	Code Type	Description
655.43	ICD-9 dx	Suspected damage to fetus from other disease in the mother, affecting management of mother, antepartum condition or complication
655.53	ICD-9 dx	Suspected damage to fetus from drugs, affecting management of mother, antepartum condition or complication
655.63	ICD-9 dx	Suspected damage to fetus from radiation, affecting management of mother, antepartum condition or complication
655.73	ICD-9 dx	Decreased fetal movements, affecting management of mother, antepartum condition or complication
655.83	ICD-9 dx	Other known or suspected fetal abnormality, not elsewhere classified, affecting management of mother, antepartum condition or complication
655.93	ICD-9 dx	Unspecified suspected fetal abnormality, affecting management of mother, antepartum condition or complication
656.03	ICD-9 dx	Fetal-maternal hemorrhage, antepartum condition or complication
656.13	ICD-9 dx	Rhesus isoimmunization, antepartum condition or complication
656.23	ICD-9 dx	Isoimmunization from other and unspecified blood-group incompatibility, antepartum condition or complication
656.33	ICD-9 dx	Fetal distress, affecting management of mother, antepartum condition or complication
656.53	ICD-9 dx	Poor fetal growth, affecting management of mother, antepartum condition or complication
656.63	ICD-9 dx	Excessive fetal growth, affecting management of mother, antepartum condition or complication
656.73	ICD-9 dx	Other placental conditions, affecting management of mother, antepartum condition or complication
656.83	ICD-9 dx	Other specified fetal and placental problems, affecting management of mother, antepartum condition or complication
656.93	ICD-9 dx	Unspecified fetal and placental problem, affecting management of mother, antepartum condition or complication
657.03	ICD-9 dx	Polyhydramnios, antepartum condition or complication
658.03	ICD-9 dx	Oligohydramnios, antepartum condition or complication
658.43	ICD-9 dx	Infection of amniotic cavity, antepartum condition or complication
658.83	ICD-9 dx	Other problems associated with amniotic cavity and membranes, antepartum
658.93	ICD-9 dx	Unspecified problem associated with amniotic cavity and membranes, antepartum condition or complication
659.43	ICD-9 dx	Grand multiparity, antepartum condition or complication
659.53	ICD-9 dx	Elderly primigravida, antepartum condition or complication
659.63	ICD-9 dx	Elderly multigravida, antepartum condition or complication
659.73	ICD-9 dx	Abnormality in fetal heart rate or rhythm, antepartum condition or complication
75.1	ICD-9 px	diagnostic amniocentesis
76801	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; single or first gestation
76802	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks 0 days), transabdominal approach; each additional gestation

Code	Code Type	Description
76805	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
76810	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; each additional gestation
76811	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation
76812	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; each additional gestation
76813	CPT	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
76814	CPT	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation
76815	CPT	Ultrasound, pregnant uterus, real time with image documentation, limited (e.g., fetal heartbeat, placental location, fetal position, and/or qualitative amniotic fluid volume), one or more fetuses
76816	CPT	Ultrasound, pregnant uterus, real time with image documentation, follow up
76817	CPT	Ultrasound, pregnant uterus, real time with image documentation, transvaginal
76818	CPT	Fetal biophysical profile; with non-stress testing
76819	CPT	Fetal biophysical profile; without non-stress testing
76820	CPT	Doppler velocimetry, fetal; umbilical artery
76821	CPT	Doppler velocimetry, fetal; middle cerebral artery
76825	CPT	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D) with or without M-mode recording
76826	CPT	Echocardiography, fetal, cardiovascular system, real time with image documentation (2D) with or without M-mode recording; follow up or repeat study
76827	CPT	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display; complete
76828	CPT	Doppler echocardiography, fetal pulsed wave and/or continuous wave with spectral display; follow up or repeat study
76941	CPT	Ultrasonic guidance imaging supervision and interpretation for transfusion or drainage of uterus
76945	CPT	Ultrasonic guidance for chorionic villus sampling
76946	CPT	Ultrasonic guidance for amniocentesis
80055	CPT	Obstetric panel
80081	CPT	Obstetric panel with HIV
81507	CPT	Fetal aneuploidy screening
82105	CPT	Alpha-fetoprotein screen, serum
82106	CPT	Alpha-fetoprotein screen, amniotic fluid
88.78	ICD-9 px	Diagnostic ultrasound of gravid uterus
BY47ZZZ	ICD-10-PCS	Ultrasonography of fetal umbilical cord

Code	Code Type	Description
BY48ZZZ	ICD-10-PCS	Ultrasonography of placenta
BY49ZZZ	ICD-10-PCS	Ultrasonography in first trimester, single fetus
BY4BZZZ	ICD-10-PCS	Ultrasonography in first trimester, multiple gestation
BY4CZZZ	ICD-10-PCS	Ultrasonography in second trimester, single fetus
BY4DZZZ	ICD-10-PCS	Ultrasonography in second trimester, multiple gestation
BY4FZZZ	ICD-10-PCS	Ultrasonography in third trimester, single fetus
BY4GZZZ	ICD-10-PCS	Ultrasonography in third trimester, multiple gestation
O09.01	ICD-10-CM	Supervision of pregnancy with history of infertility, first trimester
O09.02	ICD-10-CM	Supervision of pregnancy with history of infertility, second trimester
O09.11	ICD-10-CM	Supervision of pregnancy with history of ectopic pregnancy, first trimester
O09.12	ICD-10-CM	Supervision of pregnancy with history of ectopic pregnancy, second trimester
O09.211	ICD-10-CM	Supervision of pregnancy with history of pre-term labor, first trimester
O09.212	ICD-10-CM	Supervision of pregnancy with history of pre-term labor, second trimester
O09.291	ICD-10-CM	Supervision of pregnancy with other poor reproductive or obstetric history, first trimester
O09.292	ICD-10-CM	Supervision of pregnancy with other poor reproductive or obstetric history, second trimester
O09.31	ICD-10-CM	Supervision of pregnancy with insufficient antenatal care, first trimester
O09.32	ICD-10-CM	Supervision of pregnancy with insufficient antenatal care, second trimester
O09.41	ICD-10-CM	Supervision of pregnancy with grand multiparity, first trimester
O09.42	ICD-10-CM	Supervision of pregnancy with grand multiparity, second trimester
O09.511	ICD-10-CM	Supervision of elderly primigravida, first trimester
O09.512	ICD-10-CM	Supervision of elderly primigravida, second trimester
O09.521	ICD-10-CM	Supervision of elderly multigravida, first trimester
O09.522	ICD-10-CM	Supervision of elderly multigravida, second trimester
O09.611	ICD-10-CM	Supervision of young primigravida, first trimester
O09.612	ICD-10-CM	Supervision of young primigravida, second trimester
O09.621	ICD-10-CM	Supervision of young multigravida, first trimester
O09.622	ICD-10-CM	Supervision of young multigravida, second trimester
O09.71	ICD-10-CM	Supervision of high risk pregnancy due to social problems, first trimester
O09.72	ICD-10-CM	Supervision of high risk pregnancy due to social problems, second trimester
O09.811	ICD-10-CM	Supervision of pregnancy resulting from assisted reproductive technology, first trimester
O09.812	ICD-10-CM	Supervision of pregnancy resulting from assisted reproductive technology, second trimester
O09.821	ICD-10-CM	Supervision of pregnancy with history of in utero procedure during previous pregnancy, first trimester
O09.822	ICD-10-CM	Supervision of pregnancy with history of in utero procedure during previous pregnancy, second trimester
O09.891	ICD-10-CM	Supervision of other high risk pregnancies, first trimester
O09.892	ICD-10-CM	Supervision of other high risk pregnancies, second trimester
O09.91	ICD-10-CM	Supervision of high risk pregnancy, unspecified, first trimester

Code	Code Type	Description
O09.92	ICD-10-CM	Supervision of high risk pregnancy, unspecified, second trimester
O09.A1	ICD-10-CM	Supervision of pregnancy with history of molar pregnancy, first trimester
O09.A2	ICD-10-CM	Supervision of pregnancy with history of molar pregnancy, second trimester
O10.011	ICD-10-CM	Pre-existing essential hypertension complicating pregnancy, first trimester
O10.012	ICD-10-CM	Pre-existing essential hypertension complicating pregnancy, second trimester
O10.111	ICD-10-CM	Pre-existing hypertensive heart disease complicating pregnancy, first trimester
O10.112	ICD-10-CM	Pre-existing hypertensive heart disease complicating pregnancy, second trimester
O10.211	ICD-10-CM	Pre-existing hypertensive chronic kidney disease complicating pregnancy, first trimester
O10.212	ICD-10-CM	Pre-existing hypertensive chronic kidney disease complicating pregnancy, second trimester
O10.311	ICD-10-CM	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, first trimester
O10.312	ICD-10-CM	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, second trimester
O10.411	ICD-10-CM	Pre-existing secondary hypertension complicating pregnancy, first trimester
O10.412	ICD-10-CM	Pre-existing secondary hypertension complicating pregnancy, second trimester
O10.911	ICD-10-CM	Unspecified pre-existing hypertension complicating pregnancy, first trimester
O10.912	ICD-10-CM	Unspecified pre-existing hypertension complicating pregnancy, second trimester
O11.1	ICD-10-CM	Pre-existing hypertension with pre-eclampsia, first trimester
O11.2	ICD-10-CM	Pre-existing hypertension with pre-eclampsia, second trimester
O12.01	ICD-10-CM	Gestational edema, first trimester
O12.02	ICD-10-CM	Gestational edema, second trimester
O12.11	ICD-10-CM	Gestational proteinuria, first trimester
O12.12	ICD-10-CM	Gestational proteinuria, second trimester
O12.21	ICD-10-CM	Gestational edema with proteinuria, first trimester
O12.22	ICD-10-CM	Gestational edema with proteinuria, second trimester
O13.1	ICD-10-CM	Gestational [pregnancy-induced] hypertension without significant proteinuria, first trimester
O13.2	ICD-10-CM	Gestational [pregnancy-induced] hypertension without significant proteinuria, second trimester
O14.02	ICD-10-CM	Mild to moderate pre-eclampsia, second trimester
O14.12	ICD-10-CM	Severe pre-eclampsia, second trimester
O14.22	ICD-10-CM	HELLP syndrome (HELLP), second trimester
O14.92	ICD-10-CM	Unspecified pre-eclampsia, second trimester
O15.02	ICD-10-CM	Eclampsia complicating pregnancy, second trimester
O15.9	ICD-10-CM	Eclampsia, unspecified as to time period
O16.1	ICD-10-CM	Unspecified maternal hypertension, first trimester
O16.2	ICD-10-CM	Unspecified maternal hypertension, second trimester
O20.0	ICD-10-CM	Threatened abortion

Code	Code Type	Description
O20.8	ICD-10-CM	Other hemorrhage in early pregnancy
O20.9	ICD-10-CM	Hemorrhage in early pregnancy, unspecified
O21.0	ICD-10-CM	Mild hyperemesis gravidarum
O21.1	ICD-10-CM	Hyperemesis gravidarum with metabolic disturbance
O21.2	ICD-10-CM	Late vomiting of pregnancy
O21.8	ICD-10-CM	Other vomiting complicating pregnancy
O21.9	ICD-10-CM	Vomiting of pregnancy, unspecified
O22.01	ICD-10-CM	Varicose veins of lower extremity in pregnancy, first trimester
O22.02	ICD-10-CM	Varicose veins of lower extremity in pregnancy, second trimester
O22.11	ICD-10-CM	Genital varices in pregnancy, first trimester
O22.12	ICD-10-CM	Genital varices in pregnancy, second trimester
O22.21	ICD-10-CM	Superficial thrombophlebitis in pregnancy, first trimester
O22.22	ICD-10-CM	Superficial thrombophlebitis in pregnancy, second trimester
O22.31	ICD-10-CM	Deep phlebothrombosis in pregnancy, first trimester
O22.32	ICD-10-CM	Deep phlebothrombosis in pregnancy, second trimester
O22.41	ICD-10-CM	Hemorrhoids in pregnancy, first trimester
O22.42	ICD-10-CM	Hemorrhoids in pregnancy, second trimester
O22.51	ICD-10-CM	Cerebral venous thrombosis in pregnancy, first trimester
O22.52	ICD-10-CM	Cerebral venous thrombosis in pregnancy, second trimester
O22.8X1	ICD-10-CM	Other venous complications in pregnancy, first trimester
O22.8X2	ICD-10-CM	Other venous complications in pregnancy, second trimester
O22.91	ICD-10-CM	Venous complication in pregnancy, unspecified, first trimester
O22.92	ICD-10-CM	Venous complication in pregnancy, unspecified, second trimester
O23.01	ICD-10-CM	Infections of kidney in pregnancy, first trimester
O23.02	ICD-10-CM	Infections of kidney in pregnancy, second trimester
O23.11	ICD-10-CM	Infections of bladder in pregnancy, first trimester
O23.12	ICD-10-CM	Infections of bladder in pregnancy, second trimester
O23.21	ICD-10-CM	Infections of urethra in pregnancy, first trimester
O23.22	ICD-10-CM	Infections of urethra in pregnancy, second trimester
O23.31	ICD-10-CM	Infections of other parts of urinary tract in pregnancy, first trimester
O23.32	ICD-10-CM	Infections of other parts of urinary tract in pregnancy, second trimester
O23.41	ICD-10-CM	Unspecified infection of urinary tract in pregnancy, first trimester
O23.42	ICD-10-CM	Unspecified infection of urinary tract in pregnancy, second trimester
O23.511	ICD-10-CM	Infections of cervix in pregnancy, first trimester
O23.512	ICD-10-CM	Infections of cervix in pregnancy, second trimester
O23.521	ICD-10-CM	Salpingo-oophoritis in pregnancy, first trimester
O23.522	ICD-10-CM	Salpingo-oophoritis in pregnancy, second trimester
O23.591	ICD-10-CM	Infection of other part of genital tract in pregnancy, first trimester
O23.592	ICD-10-CM	Infection of other part of genital tract in pregnancy, second trimester
O23.91	ICD-10-CM	Unspecified genitourinary tract infection in pregnancy, first trimester
O23.92	ICD-10-CM	Unspecified genitourinary tract infection in pregnancy, second trimester

Code	Code Type	Description
O24.011	ICD-10-CM	Pre-existing type 1 diabetes mellitus, in pregnancy, first trimester
O24.012	ICD-10-CM	Pre-existing type 1 diabetes mellitus, in pregnancy, second trimester
O24.111	ICD-10-CM	Pre-existing type 2 diabetes mellitus, in pregnancy, first trimester
O24.112	ICD-10-CM	Pre-existing type 2 diabetes mellitus, in pregnancy, second trimester
O24.311	ICD-10-CM	Unspecified pre-existing diabetes mellitus in pregnancy, first trimester
O24.312	ICD-10-CM	Unspecified pre-existing diabetes mellitus in pregnancy, second trimester
O24.410	ICD-10-CM	Gestational diabetes mellitus in pregnancy, diet controlled
O24.414	ICD-10-CM	Gestational diabetes mellitus in pregnancy, insulin controlled
O24.415	ICD-10-CM	Gestational diabetes mellitus in pregnancy, controlled by oral hypoglycemic drugs
O24.419	ICD-10-CM	Gestational diabetes mellitus in pregnancy, unspecified control
O24.811	ICD-10-CM	Other pre-existing diabetes mellitus in pregnancy, first trimester
O24.812	ICD-10-CM	Other pre-existing diabetes mellitus in pregnancy, second trimester
O24.911	ICD-10-CM	Unspecified diabetes mellitus in pregnancy, first trimester
O24.912	ICD-10-CM	Unspecified diabetes mellitus in pregnancy, second trimester
O25.11	ICD-10-CM	Malnutrition in pregnancy, first trimester
O25.12	ICD-10-CM	Malnutrition in pregnancy, second trimester
O26.01	ICD-10-CM	Excessive weight gain in pregnancy, first trimester
O26.02	ICD-10-CM	Excessive weight gain in pregnancy, second trimester
O26.11	ICD-10-CM	Low weight gain in pregnancy, first trimester
O26.12	ICD-10-CM	Low weight gain in pregnancy, second trimester
O26.21	ICD-10-CM	Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22	ICD-10-CM	Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.31	ICD-10-CM	Retained intrauterine contraceptive device in pregnancy, first trimester
O26.32	ICD-10-CM	Retained intrauterine contraceptive device in pregnancy, second trimester
O26.41	ICD-10-CM	Herpes gestationis, first trimester
O26.42	ICD-10-CM	Herpes gestationis, second trimester
O26.51	ICD-10-CM	Maternal hypotension syndrome, first trimester
O26.52	ICD-10-CM	Maternal hypotension syndrome, second trimester
O26.611	ICD-10-CM	Liver and biliary tract disorders in pregnancy, first trimester
O26.612	ICD-10-CM	Liver and biliary tract disorders in pregnancy, second trimester
O26.711	ICD-10-CM	Subluxation of symphysis (pubis) in pregnancy, first trimester
O26.712	ICD-10-CM	Subluxation of symphysis (pubis) in pregnancy, second trimester
O26.811	ICD-10-CM	Pregnancy related exhaustion and fatigue, first trimester
O26.812	ICD-10-CM	Pregnancy related exhaustion and fatigue, second trimester
O26.821	ICD-10-CM	Pregnancy related peripheral neuritis, first trimester
O26.822	ICD-10-CM	Pregnancy related peripheral neuritis, second trimester
O26.831	ICD-10-CM	Pregnancy related renal disease, first trimester
O26.832	ICD-10-CM	Pregnancy related renal disease, second trimester
O26.841	ICD-10-CM	Uterine size-date discrepancy, first trimester
O26.842	ICD-10-CM	Uterine size-date discrepancy, second trimester

Code	Code Type	Description
O26.851	ICD-10-CM	Spotting complicating pregnancy, first trimester
O26.852	ICD-10-CM	Spotting complicating pregnancy, second trimester
O26.86	ICD-10-CM	Pruritic urticarial papules and plaques of pregnancy (PUPPP)
O26.872	ICD-10-CM	Cervical shortening, second trimester
O26.891	ICD-10-CM	Other specified pregnancy related conditions, first trimester
O26.892	ICD-10-CM	Other specified pregnancy related conditions, second trimester
O26.91	ICD-10-CM	Pregnancy related conditions, unspecified, first trimester
O26.92	ICD-10-CM	Pregnancy related conditions, unspecified, second trimester
O28.0	ICD-10-CM	Abnormal hematological finding on antenatal screening of mother
O28.1	ICD-10-CM	Abnormal biochemical finding on antenatal screening of mother
O28.2	ICD-10-CM	Abnormal cytological finding on antenatal screening of mother
O28.3	ICD-10-CM	Abnormal ultrasonic finding on antenatal screening of mother
O28.4	ICD-10-CM	Abnormal radiological finding on antenatal screening of mother
O28.5	ICD-10-CM	Abnormal chromosomal and genetic finding on antenatal screening of mother
O28.8	ICD-10-CM	Other abnormal findings on antenatal screening of mother
O28.9	ICD-10-CM	Unspecified abnormal findings on antenatal screening of mother
O29.011	ICD-10-CM	Aspiration pneumonitis due to anesthesia during pregnancy, first trimester
O29.012	ICD-10-CM	Aspiration pneumonitis due to anesthesia during pregnancy, second trimester
O29.021	ICD-10-CM	Pressure collapse of lung due to anesthesia during pregnancy, first trimester
O29.022	ICD-10-CM	Pressure collapse of lung due to anesthesia during pregnancy, second trimester
O29.091	ICD-10-CM	Other pulmonary complications of anesthesia during pregnancy, first trimester
O29.092	ICD-10-CM	Other pulmonary complications of anesthesia during pregnancy, second trimester
O29.111	ICD-10-CM	Cardiac arrest due to anesthesia during pregnancy, first trimester
O29.112	ICD-10-CM	Cardiac arrest due to anesthesia during pregnancy, second trimester
O29.121	ICD-10-CM	Cardiac failure due to anesthesia during pregnancy, first trimester
O29.122	ICD-10-CM	Cardiac failure due to anesthesia during pregnancy, second trimester
O29.191	ICD-10-CM	Other cardiac complications of anesthesia during pregnancy, first trimester
O29.192	ICD-10-CM	Other cardiac complications of anesthesia during pregnancy, second trimester
O29.211	ICD-10-CM	Cerebral anoxia due to anesthesia during pregnancy, first trimester
O29.212	ICD-10-CM	Cerebral anoxia due to anesthesia during pregnancy, second trimester
O29.291	ICD-10-CM	Other central nervous system complications of anesthesia during pregnancy, first trimester
O29.292	ICD-10-CM	Other central nervous system complications of anesthesia during pregnancy, second trimester
O29.3X1	ICD-10-CM	Toxic reaction to local anesthesia during pregnancy, first trimester
O29.3X2	ICD-10-CM	Toxic reaction to local anesthesia during pregnancy, second trimester
O29.41	ICD-10-CM	Spinal and epidural anesthesia induced headache during pregnancy, first trimester

Code	Code Type	Description
O29.42	ICD-10-CM	Spinal and epidural anesthesia induced headache during pregnancy, second trimester
O29.5X1	ICD-10-CM	Other complications of spinal and epidural anesthesia during pregnancy, first trimester
O29.5X2	ICD-10-CM	Other complications of spinal and epidural anesthesia during pregnancy, second trimester
O29.61	ICD-10-CM	Failed or difficult intubation for anesthesia during pregnancy, first trimester
O29.62	ICD-10-CM	Failed or difficult intubation for anesthesia during pregnancy, second trimester
O29.8X1	ICD-10-CM	Other complications of anesthesia during pregnancy, first trimester
O29.8X2	ICD-10-CM	Other complications of anesthesia during pregnancy, second trimester
O29.91	ICD-10-CM	Unspecified complication of anesthesia during pregnancy, first trimester
O29.92	ICD-10-CM	Unspecified complication of anesthesia during pregnancy, second trimester
O30.001	ICD-10-CM	Twin pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, first trimester
O30.002	ICD-10-CM	Twin pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, second trimester
O30.011	ICD-10-CM	Twin pregnancy, monochorionic/monoamniotic, first trimester
O30.012	ICD-10-CM	Twin pregnancy, monochorionic/monoamniotic, second trimester
O30.021	ICD-10-CM	Conjoined twin pregnancy, first trimester
O30.022	ICD-10-CM	Conjoined twin pregnancy, second trimester
O30.031	ICD-10-CM	Twin pregnancy, monochorionic/diamniotic, first trimester
O30.032	ICD-10-CM	Twin pregnancy, monochorionic/diamniotic, second trimester
O30.041	ICD-10-CM	Twin pregnancy, dichorionic/diamniotic, first trimester
O30.042	ICD-10-CM	Twin pregnancy, dichorionic/diamniotic, second trimester
O30.091	ICD-10-CM	Twin pregnancy, unable to determine number of placenta and number of amniotic sacs, first trimester
O30.092	ICD-10-CM	Twin pregnancy, unable to determine number of placenta and number of amniotic sacs, second trimester
O30.101	ICD-10-CM	Triplet pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, first trimester
O30.102	ICD-10-CM	Triplet pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, second trimester
O30.111	ICD-10-CM	Triplet pregnancy with two or more monochorionic fetuses, first trimester
O30.112	ICD-10-CM	Triplet pregnancy with two or more monochorionic fetuses, second trimester
O30.121	ICD-10-CM	Triplet pregnancy with two or more monoamniotic fetuses, first trimester
O30.122	ICD-10-CM	Triplet pregnancy with two or more monoamniotic fetuses, second trimester
O30.191	ICD-10-CM	Triplet pregnancy, unable to determine number of placenta and number of amniotic sacs, first trimester
O30.192	ICD-10-CM	Triplet pregnancy, unable to determine number of placenta and number of amniotic sacs, second trimester
O30.201	ICD-10-CM	Quadruplet pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, first trimester
O30.202	ICD-10-CM	Quadruplet pregnancy, unspecified number of placenta and unspecified number of amniotic sacs, second trimester
O30.211	ICD-10-CM	Quadruplet pregnancy with two or more monochorionic fetuses, first trimester

Code	Code Type	Description
O30.212	ICD-10-CM	Quadruplet pregnancy with two or more monochorionic fetuses, second trimester
O30.221	ICD-10-CM	Quadruplet pregnancy with two or more monoamniotic fetuses, first trimester
O30.222	ICD-10-CM	Quadruplet pregnancy with two or more monoamniotic fetuses, second trimester
O30.291	ICD-10-CM	Quadruplet pregnancy, unable to determine number of placenta and number of amniotic sacs, first trimester
O30.292	ICD-10-CM	Quadruplet pregnancy, unable to determine number of placenta and number of amniotic sacs, second trimester
O30.801	ICD-10-CM	Other specified multiple gestation, unspecified number of placenta and unspecified number of amniotic sacs, first trimester
O30.802	ICD-10-CM	Other specified multiple gestation, unspecified number of placenta and unspecified number of amniotic sacs, second trimester
O30.811	ICD-10-CM	Other specified multiple gestation with two or more monochorionic fetuses, first trimester
O30.812	ICD-10-CM	Other specified multiple gestation with two or more monochorionic fetuses, second trimester
O30.821	ICD-10-CM	Other specified multiple gestation with two or more monoamniotic fetuses, first trimester
O30.822	ICD-10-CM	Other specified multiple gestation with two or more monoamniotic fetuses, second trimester
O30.891	ICD-10-CM	Other specified multiple gestation, unable to determine number of placenta and number of amniotic sacs, first trimester
O30.892	ICD-10-CM	Other specified multiple gestation, unable to determine number of placenta and number of amniotic sacs, second trimester
O30.91	ICD-10-CM	Multiple gestation, unspecified, first trimester
O30.92	ICD-10-CM	Multiple gestation, unspecified, second trimester
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, not applicable or unspecified
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, fetus 1
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, fetus 2
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, fetus 3
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, fetus 4
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, fetus 5
O31.01X	ICD-10-CM	Papyraceous fetus, first trimester, other fetus
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, not applicable or unspecified
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, fetus 1
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, fetus 2
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, fetus 3
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, fetus 4
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, fetus 5
O31.02X	ICD-10-CM	Papyraceous fetus, second trimester, other fetus
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, not applicable or unspecified
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, fetus 1
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, fetus 2

Code	Code Type	Description
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, fetus 3
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, fetus 4
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, fetus 5
O31.8X1	ICD-10-CM	Other complications specific to multiple gestation, first trimester, other fetus
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, not applicable or unspecified
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, fetus 1
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, fetus 2
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, fetus 3
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, fetus 4
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, fetus 5
O31.8X2	ICD-10-CM	Other complications specific to multiple gestation, second trimester, other fetus
O34.01	ICD-10-CM	Maternal care for unspecified congenital malformation of uterus, first trimester
O34.02	ICD-10-CM	Maternal care for unspecified congenital malformation of uterus, second trimester
O34.11	ICD-10-CM	Maternal care for benign tumor of corpus uteri, first trimester
O34.12	ICD-10-CM	Maternal care for benign tumor of corpus uteri, second trimester
O34.31	ICD-10-CM	Maternal care for cervical incompetence, first trimester
O34.32	ICD-10-CM	Maternal care for cervical incompetence, second trimester
O34.41	ICD-10-CM	Maternal care for other abnormalities of cervix, first trimester
O34.42	ICD-10-CM	Maternal care for other abnormalities of cervix, second trimester
O34.511	ICD-10-CM	Maternal care for incarceration of gravid uterus, first trimester
O34.512	ICD-10-CM	Maternal care for incarceration of gravid uterus, second trimester
O34.521	ICD-10-CM	Maternal care for prolapse of gravid uterus, first trimester
O34.522	ICD-10-CM	Maternal care for prolapse of gravid uterus, second trimester
O34.531	ICD-10-CM	Maternal care for retroversion of gravid uterus, first trimester
O34.532	ICD-10-CM	Maternal care for retroversion of gravid uterus, second trimester
O34.591	ICD-10-CM	Maternal care for other abnormalities of gravid uterus, first trimester
O34.592	ICD-10-CM	Maternal care for other abnormalities of gravid uterus, second trimester
O34.61	ICD-10-CM	Maternal care for abnormality of vagina, first trimester
O34.62	ICD-10-CM	Maternal care for abnormality of vagina, second trimester
O34.71	ICD-10-CM	Maternal care for abnormality of vulva and perineum, first trimester
O34.72	ICD-10-CM	Maternal care for abnormality of vulva and perineum, second trimester
O34.81	ICD-10-CM	Maternal care for other abnormalities of pelvic organs, first trimester
O34.82	ICD-10-CM	Maternal care for other abnormalities of pelvic organs, second trimester
O34.91	ICD-10-CM	Maternal care for abnormality of pelvic organ, unspecified, first trimester
O34.92	ICD-10-CM	Maternal care for abnormality of pelvic organ, unspecified, second trimester
O36.0110	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, not applicable or unspecified
O36.0111	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, fetus 1
O36.0112	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, fetus 2

Code	Code Type	Description
O36.0113	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, fetus 3
O36.0114	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, fetus 4
O36.0115	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, fetus 5
O36.0119	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, first trimester, other fetus
O36.0120	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, not applicable or unspecified
O36.0121	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, fetus 1
O36.0122	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, fetus 2
O36.0123	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, fetus 3
O36.0124	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, fetus 4
O36.0125	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, fetus 5
O36.0129	ICD-10-CM	Maternal care for anti-D [Rh] antibodies, second trimester, other fetus
O36.0910	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, not applicable or unspecified
O36.0911	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, fetus 1
O36.0912	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, fetus 2
O36.0913	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, fetus 3
O36.0914	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, fetus 4
O36.0915	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, fetus 5
O36.0919	ICD-10-CM	Maternal care for other rhesus isoimmunization, first trimester, other fetus
O36.0920	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, not applicable or unspecified
O36.0921	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, fetus 1
O36.0922	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, fetus 2
O36.0923	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, fetus 3
O36.0924	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, fetus 4
O36.0925	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, fetus 5
O36.0929	ICD-10-CM	Maternal care for other rhesus isoimmunization, second trimester, other fetus
O36.1110	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, not applicable or unspecified
O36.1111	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, fetus 1
O36.1112	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, fetus 2
O36.1113	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, fetus 3
O36.1114	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, fetus 4
O36.1115	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, fetus 5
O36.1119	ICD-10-CM	Maternal care for Anti-A sensitization, first trimester, other fetus
O36.1120	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, not applicable or unspecified
O36.1121	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, fetus 1
O36.1122	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, fetus 2
O36.1123	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, fetus 3
O36.1124	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, fetus 4

Code	Code Type	Description
O36.1125	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, fetus 5
O36.1129	ICD-10-CM	Maternal care for Anti-A sensitization, second trimester, other fetus
O36.1910	ICD-10-CM	Maternal care for other isoimmunization, first trimester, not applicable or unspecified
O36.1911	ICD-10-CM	Maternal care for other isoimmunization, first trimester, fetus 1
O36.1912	ICD-10-CM	Maternal care for other isoimmunization, first trimester, fetus 2
O36.1913	ICD-10-CM	Maternal care for other isoimmunization, first trimester, fetus 3
O36.1914	ICD-10-CM	Maternal care for other isoimmunization, first trimester, fetus 4
O36.1915	ICD-10-CM	Maternal care for other isoimmunization, first trimester, fetus 5
O36.1919	ICD-10-CM	Maternal care for other isoimmunization, first trimester, other fetus
O36.1920	ICD-10-CM	Maternal care for other isoimmunization, second trimester, not applicable or unspecified
O36.1921	ICD-10-CM	Maternal care for other isoimmunization, second trimester, fetus 1
O36.1922	ICD-10-CM	Maternal care for other isoimmunization, second trimester, fetus 2
O36.1923	ICD-10-CM	Maternal care for other isoimmunization, second trimester, fetus 3
O36.1924	ICD-10-CM	Maternal care for other isoimmunization, second trimester, fetus 4
O36.1925	ICD-10-CM	Maternal care for other isoimmunization, second trimester, fetus 5
O36.1929	ICD-10-CM	Maternal care for other isoimmunization, second trimester, other fetus
O36.21X0	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, not applicable or unspecified
O36.21X1	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, fetus 1
O36.21X2	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, fetus 2
O36.21X3	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, fetus 3
O36.21X4	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, fetus 4
O36.21X5	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, fetus 5
O36.21X9	ICD-10-CM	Maternal care for hydrops fetalis, first trimester, other fetus
O36.22X0	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, not applicable or unspecified
O36.22X1	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, fetus 1
O36.22X2	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, fetus 2
O36.22X3	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, fetus 3
O36.22X4	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, fetus 4
O36.22X5	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, fetus 5
O36.22X9	ICD-10-CM	Maternal care for hydrops fetalis, second trimester, other fetus
O36.5110	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, not applicable or unspecified
O36.5111	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, fetus 1
O36.5112	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, fetus 2
O36.5113	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, fetus 3
O36.5114	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, fetus 4

Code	Code Type	Description
O36.5115	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, fetus 5
O36.5119	ICD-10-CM	Maternal care for known or suspected placental insufficiency, first trimester, other fetus
O36.5120	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, not applicable or unspecified
O36.5121	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, fetus 1
O36.5122	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, fetus 2
O36.5123	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, fetus 3
O36.5124	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, fetus 4
O36.5125	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, fetus 5
O36.5129	ICD-10-CM	Maternal care for known or suspected placental insufficiency, second trimester, other fetus
O36.5910	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, not applicable or unspecified
O36.5911	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 1
O36.5912	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 2
O36.5913	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 3
O36.5914	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 4
O36.5915	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 5
O36.5919	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, first trimester, other fetus
O36.5920	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, not applicable or unspecified
O36.5921	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 1
O36.5922	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 2
O36.5923	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 3
O36.5924	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 4
O36.5925	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 5
O36.5929	ICD-10-CM	Maternal care for other known or suspected poor fetal growth, second trimester, other fetus
O36.61X0	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, not applicable or unspecified
O36.61X1	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, fetus 1
O36.61X2	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, fetus 2

Code	Code Type	Description
O36.61X3	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, fetus 3
O36.61X4	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, fetus 4
O36.61X5	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, fetus 5
O36.61X9	ICD-10-CM	Maternal care for excessive fetal growth, first trimester, other fetus
O36.62X0	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, not applicable or unspecified
O36.62X1	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, fetus 1
O36.62X2	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, fetus 2
O36.62X3	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, fetus 3
O36.62X4	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, fetus 4
O36.62X5	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, fetus 5
O36.62X9	ICD-10-CM	Maternal care for excessive fetal growth, second trimester, other fetus
O36.71X0	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, not applicable or unspecified
O36.71X1	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 1
O36.71X2	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 2
O36.71X3	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 3
O36.71X4	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 4
O36.71X5	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 5
O36.71X9	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, first trimester, other fetus
O36.72X0	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, not applicable or unspecified
O36.72X1	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 1
O36.72X2	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 2
O36.72X3	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 3
O36.72X4	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 4
O36.72X5	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 5
O36.72X9	ICD-10-CM	Maternal care for viable fetus in abdominal pregnancy, second trimester, other fetus
O36.8120	ICD-10-CM	Decreased fetal movements, second trimester, not applicable or unspecified
O36.8121	ICD-10-CM	Decreased fetal movements, second trimester, fetus 1
O36.8122	ICD-10-CM	Decreased fetal movements, second trimester, fetus 2
O36.8123	ICD-10-CM	Decreased fetal movements, second trimester, fetus 3
O36.8124	ICD-10-CM	Decreased fetal movements, second trimester, fetus 4
O36.8125	ICD-10-CM	Decreased fetal movements, second trimester, fetus 5
O36.8129	ICD-10-CM	Decreased fetal movements, second trimester, other fetus
O36.8210	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, not applicable or unspecified
O36.8211	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, fetus 1

Code	Code Type	Description
O36.8212	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, fetus 2
O36.8213	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, fetus 3
O36.8214	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, fetus 4
O36.8215	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, fetus 5
O36.8219	ICD-10-CM	Fetal anemia and thrombocytopenia, first trimester, other fetus
O36.8220	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, not applicable or unspecified
O36.8221	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, fetus 1
O36.8222	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, fetus 2
O36.8223	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, fetus 3
O36.8224	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, fetus 4
O36.8225	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, fetus 5
O36.8229	ICD-10-CM	Fetal anemia and thrombocytopenia, second trimester, other fetus
O36.8910	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, not applicable or unspecified
O36.8911	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, fetus 1
O36.8912	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, fetus 2
O36.8913	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, fetus 3
O36.8914	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, fetus 4
O36.8915	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, fetus 5
O36.8919	ICD-10-CM	Maternal care for other specified fetal problems, first trimester, other fetus
O36.8920	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, not applicable or unspecified
O36.8921	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, fetus 1
O36.8922	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, fetus 2
O36.8923	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, fetus 3
O36.8924	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, fetus 4
O36.8925	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, fetus 5
O36.8929	ICD-10-CM	Maternal care for other specified fetal problems, second trimester, other fetus
O36.91X0	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, not applicable or unspecified
O36.91X1	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, fetus 1
O36.91X2	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, fetus 2
O36.91X3	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, fetus 3
O36.91X4	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, fetus 4
O36.91X5	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, fetus 5
O36.91X9	ICD-10-CM	Maternal care for fetal problem, unspecified, first trimester, other fetus
O36.92X0	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, not applicable or unspecified
O36.92X1	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, fetus 1
O36.92X2	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, fetus 2
O36.92X3	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, fetus 3

Code	Code Type	Description
O36.92X4	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, fetus 4
O36.92X5	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, fetus 5
O36.92X9	ICD-10-CM	Maternal care for fetal problem, unspecified, second trimester, other fetus
O40.1XX0	ICD-10-CM	Polyhydramnios, first trimester, not applicable or unspecified
O40.1XX1	ICD-10-CM	Polyhydramnios, first trimester, fetus 1
O40.1XX2	ICD-10-CM	Polyhydramnios, first trimester, fetus 2
O40.1XX3	ICD-10-CM	Polyhydramnios, first trimester, fetus 3
O40.1XX4	ICD-10-CM	Polyhydramnios, first trimester, fetus 4
O40.1XX5	ICD-10-CM	Polyhydramnios, first trimester, fetus 5
O40.1XX9	ICD-10-CM	Polyhydramnios, first trimester, other fetus
O40.2XX0	ICD-10-CM	Polyhydramnios, second trimester, not applicable or unspecified
O40.2XX1	ICD-10-CM	Polyhydramnios, second trimester, fetus 1
O40.2XX2	ICD-10-CM	Polyhydramnios, second trimester, fetus 2
O40.2XX3	ICD-10-CM	Polyhydramnios, second trimester, fetus 3
O40.2XX4	ICD-10-CM	Polyhydramnios, second trimester, fetus 4
O40.2XX5	ICD-10-CM	Polyhydramnios, second trimester, fetus 5
O40.2XX9	ICD-10-CM	Polyhydramnios, second trimester, other fetus
O41.01X0	ICD-10-CM	Oligohydramnios, first trimester, not applicable or unspecified
O41.01X1	ICD-10-CM	Oligohydramnios, first trimester, fetus 1
O41.01X2	ICD-10-CM	Oligohydramnios, first trimester, fetus 2
O41.01X3	ICD-10-CM	Oligohydramnios, first trimester, fetus 3
O41.01X4	ICD-10-CM	Oligohydramnios, first trimester, fetus 4
O41.01X5	ICD-10-CM	Oligohydramnios, first trimester, fetus 5
O41.01X9	ICD-10-CM	Oligohydramnios, first trimester, other fetus
O41.02X0	ICD-10-CM	Oligohydramnios, second trimester, not applicable or unspecified
O41.02X1	ICD-10-CM	Oligohydramnios, second trimester, fetus 1
O41.02X2	ICD-10-CM	Oligohydramnios, second trimester, fetus 2
O41.02X3	ICD-10-CM	Oligohydramnios, second trimester, fetus 3
O41.02X4	ICD-10-CM	Oligohydramnios, second trimester, fetus 4
O41.02X5	ICD-10-CM	Oligohydramnios, second trimester, fetus 5
O41.02X9	ICD-10-CM	Oligohydramnios, second trimester, other fetus
O41.1010	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, not applicable or unspecified
O41.1011	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 1
O41.1012	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 2
O41.1013	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 3
O41.1014	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 4
O41.1015	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 5
O41.1019	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, first trimester, other fetus
O41.1020	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, not applicable or unspecified

Code	Code Type	Description
O41.1021	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 1
O41.1022	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 2
O41.1023	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 3
O41.1024	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 4
O41.1025	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 5
O41.1029	ICD-10-CM	Infection of amniotic sac and membranes, unspecified, second trimester, other fetus
O41.1210	ICD-10-CM	Chorioamnionitis, first trimester, not applicable or unspecified
O41.1211	ICD-10-CM	Chorioamnionitis, first trimester, fetus 1
O41.1212	ICD-10-CM	Chorioamnionitis, first trimester, fetus 2
O41.1213	ICD-10-CM	Chorioamnionitis, first trimester, fetus 3
O41.1214	ICD-10-CM	Chorioamnionitis, first trimester, fetus 4
O41.1215	ICD-10-CM	Chorioamnionitis, first trimester, fetus 5
O41.1219	ICD-10-CM	Chorioamnionitis, first trimester, other fetus
O41.1220	ICD-10-CM	Chorioamnionitis, second trimester, not applicable or unspecified
O41.1221	ICD-10-CM	Chorioamnionitis, second trimester, fetus 1
O41.1222	ICD-10-CM	Chorioamnionitis, second trimester, fetus 2
O41.1223	ICD-10-CM	Chorioamnionitis, second trimester, fetus 3
O41.1224	ICD-10-CM	Chorioamnionitis, second trimester, fetus 4
O41.1225	ICD-10-CM	Chorioamnionitis, second trimester, fetus 5
O41.1229	ICD-10-CM	Chorioamnionitis, second trimester, other fetus
O41.1410	ICD-10-CM	Placentitis, first trimester, not applicable or unspecified
O41.1411	ICD-10-CM	Placentitis, first trimester, fetus 1
O41.1412	ICD-10-CM	Placentitis, first trimester, fetus 2
O41.1413	ICD-10-CM	Placentitis, first trimester, fetus 3
O41.1414	ICD-10-CM	Placentitis, first trimester, fetus 4
O41.1415	ICD-10-CM	Placentitis, first trimester, fetus 5
O41.1419	ICD-10-CM	Placentitis, first trimester, other fetus
O41.1420	ICD-10-CM	Placentitis, second trimester, not applicable or unspecified
O41.1421	ICD-10-CM	Placentitis, second trimester, fetus 1
O41.1422	ICD-10-CM	Placentitis, second trimester, fetus 2
O41.1423	ICD-10-CM	Placentitis, second trimester, fetus 3
O41.1424	ICD-10-CM	Placentitis, second trimester, fetus 4
O41.1425	ICD-10-CM	Placentitis, second trimester, fetus 5
O41.1429	ICD-10-CM	Placentitis, second trimester, other fetus
O41.8X10	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, not applicable or unspecified
O41.8X11	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 1

Code	Code Type	Description
O41.8X12	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 2
O41.8X13	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 3
O41.8X14	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 4
O41.8X15	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 5
O41.8X19	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, first trimester, other fetus
O41.8X20	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, not applicable or unspecified
O41.8X21	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 1
O41.8X22	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 2
O41.8X23	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 3
O41.8X24	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 4
O41.8X25	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 5
O41.8X29	ICD-10-CM	Other specified disorders of amniotic fluid and membranes, second trimester, other fetus
O41.91X0	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, not applicable or unspecified
O41.91X1	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 1
O41.91X2	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 2
O41.91X3	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 3
O41.91X4	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 4
O41.91X5	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 5
O41.91X9	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, first trimester, other fetus
O41.92X0	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, not applicable or unspecified
O41.92X1	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 1
O41.92X2	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 2
O41.92X3	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 3
O41.92X4	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 4
O41.92X5	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 5

Code	Code Type	Description
O41.92X9	ICD-10-CM	Disorder of amniotic fluid and membranes, unspecified, second trimester, other fetus
O43.011	ICD-10-CM	Fetomaternal placental transfusion syndrome, first trimester
O43.012	ICD-10-CM	Fetomaternal placental transfusion syndrome, second trimester
O43.021	ICD-10-CM	Fetus-to-fetus placental transfusion syndrome, first trimester
O43.022	ICD-10-CM	Fetus-to-fetus placental transfusion syndrome, second trimester
O43.101	ICD-10-CM	Malformation of placenta, unspecified, first trimester
O43.102	ICD-10-CM	Malformation of placenta, unspecified, second trimester
O43.111	ICD-10-CM	Circumvallate placenta, first trimester
O43.112	ICD-10-CM	Circumvallate placenta, second trimester
O43.121	ICD-10-CM	Velamentous insertion of umbilical cord, first trimester
O43.122	ICD-10-CM	Velamentous insertion of umbilical cord, second trimester
O43.191	ICD-10-CM	Other malformation of placenta, first trimester
O43.192	ICD-10-CM	Other malformation of placenta, second trimester
O43.211	ICD-10-CM	Placenta accreta, first trimester
O43.212	ICD-10-CM	Placenta accreta, second trimester
O43.221	ICD-10-CM	Placenta increta, first trimester
O43.222	ICD-10-CM	Placenta increta, second trimester
O43.231	ICD-10-CM	Placenta percreta, first trimester
O43.232	ICD-10-CM	Placenta percreta, second trimester
O43.811	ICD-10-CM	Placental infarction, first trimester
O43.812	ICD-10-CM	Placental infarction, second trimester
O43.891	ICD-10-CM	Other placental disorders, first trimester
O43.892	ICD-10-CM	Other placental disorders, second trimester
O43.91	ICD-10-CM	Unspecified placental disorder, first trimester
O43.92	ICD-10-CM	Unspecified placental disorder, second trimester
O44.01	ICD-10-CM	Complete placenta previa NOS or without hemorrhage, first trimester
O44.02	ICD-10-CM	Complete placenta previa NOS or without hemorrhage, second trimester
O44.11	ICD-10-CM	Complete placenta previa with hemorrhage, first trimester
O44.12	ICD-10-CM	Complete placenta previa with hemorrhage, second trimester
O44.21	ICD-10-CM	Partial placenta previa NOS or without hemorrhage, first trimester
O44.22	ICD-10-CM	Partial placenta previa NOS or without hemorrhage, second trimester
O44.31	ICD-10-CM	Partial placenta previa with hemorrhage, first trimester
O44.32	ICD-10-CM	Partial placenta previa with hemorrhage, second trimester
O44.41	ICD-10-CM	Low lying placenta NOS or without hemorrhage, first trimester
O44.42	ICD-10-CM	Low lying placenta NOS or without hemorrhage, second trimester
O44.51	ICD-10-CM	Low lying placenta with hemorrhage, first trimester
O44.52	ICD-10-CM	Low lying placenta with hemorrhage, second trimester
O45.001	ICD-10-CM	Premature separation of placenta with coagulation defect, unspecified, first trimester
O45.002	ICD-10-CM	Premature separation of placenta with coagulation defect, unspecified, second trimester

Code	Code Type	Description
O45.011	ICD-10-CM	Premature separation of placenta with afibrinogenemia, first trimester
O45.012	ICD-10-CM	Premature separation of placenta with afibrinogenemia, second trimester
O45.021	ICD-10-CM	Premature separation of placenta with disseminated intravascular coagulation, first trimester
O45.022	ICD-10-CM	Premature separation of placenta with disseminated intravascular coagulation, second trimester
O45.091	ICD-10-CM	Premature separation of placenta with other coagulation defect, first trimester
O45.092	ICD-10-CM	Premature separation of placenta with other coagulation defect, second trimester
O45.8X1	ICD-10-CM	Other premature separation of placenta, first trimester
O45.8X2	ICD-10-CM	Other premature separation of placenta, second trimester
O45.91	ICD-10-CM	Premature separation of placenta, unspecified, first trimester
O45.92	ICD-10-CM	Premature separation of placenta, unspecified, second trimester
O46.001	ICD-10-CM	Antepartum hemorrhage with coagulation defect, unspecified, first trimester
O46.002	ICD-10-CM	Antepartum hemorrhage with coagulation defect, unspecified, second trimester
O46.011	ICD-10-CM	Antepartum hemorrhage with afibrinogenemia, first trimester
O46.012	ICD-10-CM	Antepartum hemorrhage with afibrinogenemia, second trimester
O46.021	ICD-10-CM	Antepartum hemorrhage with disseminated intravascular coagulation, first trimester
O46.022	ICD-10-CM	Antepartum hemorrhage with disseminated intravascular coagulation, second trimester
O46.091	ICD-10-CM	Antepartum hemorrhage with other coagulation defect, first trimester
O46.092	ICD-10-CM	Antepartum hemorrhage with other coagulation defect, second trimester
O46.8X1	ICD-10-CM	Other antepartum hemorrhage, first trimester
O46.8X2	ICD-10-CM	Other antepartum hemorrhage, second trimester
O46.91	ICD-10-CM	Antepartum hemorrhage, unspecified, first trimester
O46.92	ICD-10-CM	Antepartum hemorrhage, unspecified, second trimester
O47.02	ICD-10-CM	False labor before 37 completed weeks of gestation, second trimester
O98.011	ICD-10-CM	Tuberculosis complicating pregnancy, first trimester
O98.012	ICD-10-CM	Tuberculosis complicating pregnancy, second trimester
O98.111	ICD-10-CM	Syphilis complicating pregnancy, first trimester
O98.112	ICD-10-CM	Syphilis complicating pregnancy, second trimester
O98.211	ICD-10-CM	Gonorrhea complicating pregnancy, first trimester
O98.212	ICD-10-CM	Gonorrhea complicating pregnancy, second trimester
O98.311	ICD-10-CM	Other infections with a predominantly sexual mode of transmission complicating pregnancy, first trimester
O98.312	ICD-10-CM	Other infections with a predominantly sexual mode of transmission complicating pregnancy, second trimester
O98.411	ICD-10-CM	Viral hepatitis complicating pregnancy, first trimester
O98.412	ICD-10-CM	Viral hepatitis complicating pregnancy, second trimester
O98.511	ICD-10-CM	Other viral diseases complicating pregnancy, first trimester
O98.512	ICD-10-CM	Other viral diseases complicating pregnancy, second trimester

Code	Code Type	Description
O98.611	ICD-10-CM	Protozoal diseases complicating pregnancy, first trimester
O98.612	ICD-10-CM	Protozoal diseases complicating pregnancy, second trimester
O98.711	ICD-10-CM	Human immunodeficiency virus [HIV] disease complicating pregnancy, first trimester
O98.712	ICD-10-CM	Human immunodeficiency virus [HIV] disease complicating pregnancy, second trimester
O98.811	ICD-10-CM	Other maternal infectious and parasitic diseases complicating pregnancy, first trimester
O98.812	ICD-10-CM	Other maternal infectious and parasitic diseases complicating pregnancy, second trimester
O98.911	ICD-10-CM	Unspecified maternal infectious and parasitic disease complicating pregnancy, first trimester
O98.912	ICD-10-CM	Unspecified maternal infectious and parasitic disease complicating pregnancy, second trimester
O99.011	ICD-10-CM	Anemia complicating pregnancy, first trimester
O99.012	ICD-10-CM	Anemia complicating pregnancy, second trimester
O99.111	ICD-10-CM	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy, first trimester
O99.112	ICD-10-CM	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy, second trimester
O99.211	ICD-10-CM	Obesity complicating pregnancy, first trimester
O99.212	ICD-10-CM	Obesity complicating pregnancy, second trimester
O99.281	ICD-10-CM	Endocrine, nutritional and metabolic diseases complicating pregnancy, first trimester
O99.282	ICD-10-CM	Endocrine, nutritional and metabolic diseases complicating pregnancy, second trimester
O99.311	ICD-10-CM	Alcohol use complicating pregnancy, first trimester
O99.312	ICD-10-CM	Alcohol use complicating pregnancy, second trimester
O99.321	ICD-10-CM	Drug use complicating pregnancy, first trimester
O99.322	ICD-10-CM	Drug use complicating pregnancy, second trimester
O99.331	ICD-10-CM	Smoking (tobacco) complicating pregnancy, first trimester
O99.332	ICD-10-CM	Smoking (tobacco) complicating pregnancy, second trimester
O99.341	ICD-10-CM	Other mental disorders complicating pregnancy, first trimester
O99.342	ICD-10-CM	Other mental disorders complicating pregnancy, second trimester
O99.351	ICD-10-CM	Diseases of the nervous system complicating pregnancy, first trimester
O99.352	ICD-10-CM	Diseases of the nervous system complicating pregnancy, second trimester
O99.411	ICD-10-CM	Diseases of the circulatory system complicating pregnancy, first trimester
O99.412	ICD-10-CM	Diseases of the circulatory system complicating pregnancy, second trimester
O99.511	ICD-10-CM	Diseases of the respiratory system complicating pregnancy, first trimester
O99.512	ICD-10-CM	Diseases of the respiratory system complicating pregnancy, second trimester
O99.611	ICD-10-CM	Diseases of the digestive system complicating pregnancy, first trimester
O99.612	ICD-10-CM	Diseases of the digestive system complicating pregnancy, second trimester
O99.711	ICD-10-CM	Diseases of the skin and subcutaneous tissue complicating pregnancy, first trimester

Code	Code Type	Description
O99.712	ICD-10-CM	Diseases of the skin and subcutaneous tissue complicating pregnancy, second trimester
O99.810	ICD-10-CM	Abnormal glucose complicating pregnancy
O99.820	ICD-10-CM	Streptococcus B carrier state complicating pregnancy
O99.830	ICD-10-CM	Other infection carrier state complicating pregnancy
O99.841	ICD-10-CM	Bariatric surgery status complicating pregnancy, first trimester
O99.842	ICD-10-CM	Bariatric surgery status complicating pregnancy, second trimester
O99.89	ICD-10-CM	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium
O9A.111	ICD-10-CM	Malignant neoplasm complicating pregnancy, first trimester
O9A.112	ICD-10-CM	Malignant neoplasm complicating pregnancy, second trimester
O9A.211	ICD-10-CM	Injury, poisoning and certain other consequences of external causes complicating pregnancy, first trimester
O9A.212	ICD-10-CM	Injury, poisoning and certain other consequences of external causes complicating pregnancy, second trimester
O9A.311	ICD-10-CM	Physical abuse complicating pregnancy, first trimester
O9A.312	ICD-10-CM	Physical abuse complicating pregnancy, second trimester
O9A.411	ICD-10-CM	Sexual abuse complicating pregnancy, first trimester
O9A.412	ICD-10-CM	Sexual abuse complicating pregnancy, second trimester
O9A.511	ICD-10-CM	Psychological abuse complicating pregnancy, first trimester
O9A.512	ICD-10-CM	Psychological abuse complicating pregnancy, second trimester
V22.0	ICD-9 dx	Supervision of normal first pregnancy
V22.1	ICD-9 dx	Supervision of other normal pregnancy
V22.2	ICD-9 dx	Pregnant state, incidental
V23.0	ICD-9 dx	Supervision of high-risk pregnancy with history of infertility
V23.1	ICD-9 dx	Supervision of high-risk pregnancy with history of trophoblastic disease
V23.2	ICD-9 dx	Supervision of high-risk pregnancy with history of abortion
V23.3	ICD-9 dx	Supervision of high-risk pregnancy with grand multiparity
V23.41	ICD-9 dx	Pregnancy with history of pre-term labor
V23.42	ICD-9 dx	Pregnancy with history of ectopic pregnancy
V23.49	ICD-9 dx	Pregnancy with other poor obstetric history
V23.5	ICD-9 dx	Supervision of high-risk pregnancy with other poor reproductive history
V23.6	ICD-9 dx	supervision of high risk pregnancy
V23.7	ICD-9 dx	Supervision of high-risk pregnancy with insufficient prenatal care
V23.81	ICD-9 dx	Supervision of high-risk pregnancy with elderly primigravida
V23.82	ICD-9 dx	Supervision of high-risk pregnancy with elderly multigravida
V23.83	ICD-9 dx	Supervision of high-risk pregnancy with young primigravida
V23.84	ICD-9 dx	Supervision of high-risk pregnancy with young multigravida
V23.85	ICD-9 dx	Pregnancy resulting from assisted reproductive technology
V23.86	ICD-9 dx	Pregnancy with history of in utero procedure during previous pregnancy
V23.89	ICD-9 dx	Supervision of other high-risk pregnancy
V23.9	ICD-9 dx	Supervision of unspecified high-risk pregnancy

Code	Code Type	Description
V28.0	ICD-9 dx	Antenatal screening for chromosomal anomalies by amniocentesis
V28.1	ICD-9 dx	Antenatal screening for raised alpha-fetoprotein levels in amniotic fluid
V28.2	ICD-9 dx	Other antenatal screening based on amniocentesis
V28.3	ICD-9 dx	Encounter for routine screening for malformation using ultrasonics
V28.4	ICD-9 dx	Antenatal screening for fetal growth retardation using ultrasonics
V28.5	ICD-9 dx	Antenatal screening for isoimmunization
V28.6	ICD-9 dx	Antenatal screening for Streptococcus B
V28.81	ICD-9 dx	Encounter for fetal anatomic survey
V28.82	ICD-9 dx	Encounter for screening for risk of pre-term labor
V28.89	ICD-9 dx	Other specified antenatal screening
V28.9	ICD-9 dx	Unspecified antenatal screening
V72.42	ICD-9 dx	encounter for positive pregnancy test
V91.00	ICD-9 dx	Twin gestation, unspecified number of placenta, unspecified number of amniotic sacs
V91.01	ICD-9 dx	Twin gestation, monochorionic/monoamniotic (one placenta, one amniotic sac)
V91.02	ICD-9 dx	Twin gestation, monochorionic/diamniotic (one placenta, two amniotic sacs)
V91.03	ICD-9 dx	Twin gestation, dichorionic/diamniotic (two placentae, two amniotic sacs)
V91.09	ICD-9 dx	Twin gestation, unable to determine number of placenta and number of amniotic sacs
V91.10	ICD-9 dx	Triplet gestation, unspecified number of placenta and unspecified number of amniotic sacs
V91.11	ICD-9 dx	Triplet gestation, with two or more monochorionic fetuses
V91.12	ICD-9 dx	Triplet gestation, with two or more monoamniotic fetuses
V91.19	ICD-9 dx	Triplet gestation, unable to determine number of placenta and number of amniotic sacs
V91.20	ICD-9 dx	Quadruplet gestation, unspecified number of placenta and unspecified number of amniotic sacs
V91.21	ICD-9 dx	Quadruplet gestation, with two or more monochorionic fetuses
V91.22	ICD-9 dx	Quadruplet gestation, with two or more monoamniotic fetuses
V91.29	ICD-9 dx	Quadruplet gestation, unable to determine number of placenta and number of amniotic sacs
V91.90	ICD-9 dx	Other specified multiple gestation, unspecified number of placenta and unspecified number of amniotic sacs
V91.91	ICD-9 dx	Other specified multiple gestation, with two or more monochorionic fetuses
V91.92	ICD-9 dx	Other specified multiple gestation, with two or more monoamniotic fetuses
V91.99	ICD-9 dx	Other specified multiple gestation, unable to determine number of placenta and number of amniotic sacs
Z32.01	ICD-10-CM	Encounter for pregnancy test, result positive
Z33.1	ICD-10-CM	Pregnant state, incidental
Z33.3	ICD-10-CM	Pregnant state, gestational carrier
Z34.01	ICD-10-CM	Encounter for supervision of normal first pregnancy, first trimester
Z34.02	ICD-10-CM	Encounter for supervision of normal first pregnancy, second trimester
Z34.81	ICD-10-CM	Encounter for supervision of other normal pregnancy, first trimester

Code	Code Type	Description
Z34.82	ICD-10-CM	Encounter for supervision of other normal pregnancy, second trimester
Z34.91	ICD-10-CM	Encounter for supervision of normal pregnancy, unspecified, first trimester
Z34.92	ICD-10-CM	Encounter for supervision of normal pregnancy, unspecified, second trimester
Z36.0	ICD-10-CM	Encounter for antenatal screening
Z36.1	ICD-10-CM	Encounter for antenatal screening
Z36.2	ICD-10-CM	Encounter for antenatal screening
Z36.3	ICD-10-CM	Encounter for antenatal screening
Z36.4	ICD-10-CM	Encounter for antenatal screening
Z36.5	ICD-10-CM	Encounter for antenatal screening
Z36.81	ICD-10-CM	Encounter for antenatal screening
Z36.82	ICD-10-CM	Encounter for antenatal screening
Z36.83	ICD-10-CM	Encounter for antenatal screening
Z36.84	ICD-10-CM	Encounter for antenatal screening
Z36.85	ICD-10-CM	Encounter for antenatal screening
Z36.86	ICD-10-CM	Encounter for antenatal screening
Z36.87	ICD-10-CM	Encounter for antenatal screening
Z36.88	ICD-10-CM	Encounter for antenatal screening
Z36.89	ICD-10-CM	Encounter for antenatal screening
Z36.8A	ICD-10-CM	Encounter for antenatal screening
Z36.9	ICD-10-CM	Encounter for antenatal screening
Z36	ICD-10-CM	Encounter for antenatal screening of mother
Z3A.01	ICD-10-CM	Less than 8 weeks gestation of pregnancy
Z3A.08	ICD-10-CM	8 weeks gestation of pregnancy
Z3A.09	ICD-10-CM	9 weeks gestation of pregnancy
Z3A.10	ICD-10-CM	10 weeks gestation of pregnancy
Z3A.11	ICD-10-CM	11 weeks gestation of pregnancy
Z3A.12	ICD-10-CM	12 weeks gestation of pregnancy
Z3A.13	ICD-10-CM	13 weeks gestation of pregnancy
Z3A.14	ICD-10-CM	14 weeks gestation of pregnancy
Z3A.15	ICD-10-CM	15 weeks gestation of pregnancy
Z3A.16	ICD-10-CM	16 weeks gestation of pregnancy
Z3A.17	ICD-10-CM	17 weeks gestation of pregnancy
Z3A.18	ICD-10-CM	18 weeks gestation of pregnancy
Z3A.19	ICD-10-CM	19 weeks gestation of pregnancy
Z3A.20	ICD-10-CM	20 weeks gestation of pregnancy

Table D.2: Diagnosis codes used to assign gestational age

Code	Code Type	Description	Assigned gestational age (days)
644.21	ICD-9 dx	Early onset of delivery, delivered, with or without mention of antepartum condition	245
645.10	ICD-9 dx	Post term pregnancy, unspecified as to episode of care or not applicable	287
645.11	ICD-9 dx	Post term pregnancy, delivered, with or without mention of antepartum condition	287
645.13	ICD-9 dx	Post term pregnancy, antepartum condition or complication	287
645.20	ICD-9 dx	Prolonged pregnancy, unspecified as to episode of care or not applicable	294
645.21	ICD-9 dx	Prolonged pregnancy, delivered, with or without mention of antepartum condition	294
645.23	ICD-9 dx	Prolonged pregnancy, antepartum condition or complication	294
765.00	ICD-9 dx	Extreme immaturity, unspecified [weight]	196
765.01	ICD-9 dx	Extreme immaturity, less than 500 grams	196
765.02	ICD-9 dx	Extreme immaturity, 500-749 grams	196
765.03	ICD-9 dx	Extreme immaturity, 750-999 grams	196
765.04	ICD-9 dx	Extreme immaturity, 1,000-1,249 grams	196
765.05	ICD-9 dx	Extreme immaturity, 1,250-1,499 grams	196
765.06	ICD-9 dx	Extreme immaturity, 1,500-1,749 grams	196
765.07	ICD-9 dx	Extreme immaturity, 1,750-1,999 grams	196
765.08	ICD-9 dx	Extreme immaturity, 2,000-2,499 grams	196
765.09	ICD-9 dx	Extreme immaturity, 2,500 grams and over	196
765.10	ICD-9 dx	Other preterm infants, unspecified [weight]	245
765.11	ICD-9 dx	Other preterm infants, less than 500 grams	245
765.12	ICD-9 dx	Other preterm infants, 500-749 grams	245
765.13	ICD-9 dx	Other preterm infants, 750-999 grams	245
765.14	ICD-9 dx	Other preterm infants, 1,000-1,249 grams	245
765.15	ICD-9 dx	Other preterm infants, 1,250-1,499 grams	245
765.16	ICD-9 dx	Other preterm infants, 1,500-1,749 grams	245
765.17	ICD-9 dx	Other preterm infants, 1,750-1,999 grams	245
765.18	ICD-9 dx	Other preterm infants, 2,000-2,499 grams	245
765.19	ICD-9 dx	Other preterm infants, 2,500 grams and over	245
765.20	ICD-9 dx	Unspecified weeks of gestation	245
765.21	ICD-9 dx	Less than 24 completed weeks of gestation	168
765.22	ICD-9 dx	24 completed weeks of gestation	168
765.23	ICD-9 dx	25-26 completed weeks of gestation	182
765.24	ICD-9 dx	27-28 completed weeks of gestation	196
765.25	ICD-9 dx	29-30 completed weeks of gestation	210
765.26	ICD-9 dx	31-32 completed weeks of gestation	224

Code	Code Type	Description	Assigned gestational age (days)
765.27	ICD-9 dx	33-34 completed weeks of gestation	238
765.28	ICD-9 dx	35-36 completed weeks of gestation	252
766.21	ICD-9 dx	Post-term infant	287
766.22	ICD-9 dx	Prolonged gestation of infant	294
O48.0	ICD-10-CM	Post-term pregnancy	287
O48.1	ICD-10-CM	Prolonged pregnancy	294
O60.12X0	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, not applicable or unspecified	168
O60.12X1	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 1	168
O60.12X2	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 2	168
O60.12X3	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 3	168
O60.12X4	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 4	168
O60.12X5	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 5	168
O60.12X9	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, other fetus	168
O60.13X0	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, not applicable or unspecified	245
O60.13X1	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 1	245
O60.13X2	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 2	245
O60.13X3	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 3	245
O60.13X4	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 4	245
O60.13X5	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 5	245
O60.13X9	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, other fetus	245
O60.14X0	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, not applicable or unspecified	245
O60.14X1	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 1	245
O60.14X2	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 2	245
O60.14X3	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 3	245
O60.14X4	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 4	245
O60.14X5	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 5	245
O60.14X9	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, other fetus	245

Code	Code Type	Description	Assigned gestational age (days)
P07.20	ICD-10-CM	Extreme immaturity of newborn, unspecified weeks of gestation	196
P07.21	ICD-10-CM	Extreme immaturity of newborn, gestational age less than 23 completed weeks	158
P07.22	ICD-10-CM	Extreme immaturity of newborn, gestational age 23 completed weeks	165
P07.23	ICD-10-CM	Extreme immaturity of newborn, gestational age 24 completed weeks	172
P07.24	ICD-10-CM	Extreme immaturity of newborn, gestational age 25 completed weeks	179
P07.25	ICD-10-CM	Extreme immaturity of newborn, gestational age 26 completed weeks	186
P07.26	ICD-10-CM	Extreme immaturity of newborn, gestational age 27 completed weeks	193
P07.30	ICD-10-CM	Preterm newborn, unspecified weeks of gestation	245
P07.31	ICD-10-CM	Preterm newborn, gestational age 28 completed weeks	200
P07.32	ICD-10-CM	Preterm newborn, gestational age 29 completed weeks	207
P07.33	ICD-10-CM	Preterm newborn, gestational age 30 completed weeks	214
P07.34	ICD-10-CM	Preterm newborn, gestational age 31 completed weeks	221
P07.35	ICD-10-CM	Preterm newborn, gestational age 32 completed weeks	228
P07.36	ICD-10-CM	Preterm newborn, gestational age 33 completed weeks	235
P07.37	ICD-10-CM	Preterm newborn, gestational age 34 completed weeks	242
P07.38	ICD-10-CM	Preterm newborn, gestational age 35 completed weeks	249
P07.39	ICD-10-CM	Preterm newborn, gestational age 36 completed weeks	256
P08.21	ICD-10-CM	Post-term newborn	287
P08.22	ICD-10-CM	Prolonged gestation of newborn	294
Z3A.20	ICD-10-CM	20 weeks gestation of pregnancy	144
Z3A.21	ICD-10-CM	21 weeks gestation of pregnancy	151
Z3A.22	ICD-10-CM	22 weeks gestation of pregnancy	158
Z3A.23	ICD-10-CM	23 weeks gestation of pregnancy	165
Z3A.24	ICD-10-CM	24 weeks gestation of pregnancy	172
Z3A.25	ICD-10-CM	25 weeks gestation of pregnancy	179
Z3A.26	ICD-10-CM	26 weeks gestation of pregnancy	186
Z3A.27	ICD-10-CM	27 weeks gestation of pregnancy	193
Z3A.28	ICD-10-CM	28 weeks gestation of pregnancy	200
Z3A.29	ICD-10-CM	29 weeks gestation of pregnancy	207
Z3A.30	ICD-10-CM	30 weeks gestation of pregnancy	214

Code	Code Type	Description	Assigned gestational age (days)
Z3A.31	ICD-10-CM	31 weeks gestation of pregnancy	221
Z3A.32	ICD-10-CM	32 weeks gestation of pregnancy	228
Z3A.33	ICD-10-CM	33 weeks gestation of pregnancy	235
Z3A.34	ICD-10-CM	34 weeks gestation of pregnancy	242
Z3A.35	ICD-10-CM	35 weeks gestation of pregnancy	249
Z3A.36	ICD-10-CM	36 weeks gestation of pregnancy	256
Z3A.37	ICD-10-CM	37 weeks gestation of pregnancy	263
Z3A.38	ICD-10-CM	38 weeks gestation of pregnancy	270
Z3A.39	ICD-10-CM	39 weeks gestation of pregnancy	277
Z3A.40	ICD-10-CM	40 weeks gestation of pregnancy	284
Z3A.41	ICD-10-CM	41 weeks gestation of pregnancy	291
Z3A.42	ICD-10-CM	42 weeks gestation of pregnancy	298
Z3A.49	ICD-10-CM	Greater than 42 weeks gestation of pregnancy	301

Table D.3. Diagnosis and procedure codes used to identify miscarriages

Code	Code type	Description
632	ICD-9 diagnosis	Missed abortion
634.00-634.92	ICD-9 diagnosis	Spontaneous abortion, incomplete, complete, and unspecified
637.00-637.92	ICD-9 diagnosis	Unspecified abortion, incomplete, complete, and unspecified
O02.1	ICD-10 diagnosis	Missed abortion
O03.0-O03.9	ICD-10 diagnosis	Spontaneous abortion, incomplete, complete, and unspecified
59812	CPT	Treatment of incomplete abortion, any trimester, completed surgically
59820	CPT	Treatment of missed abortion; completed surgically, first trimester
59821	CPT	Treatment of missed abortion; completed surgically, second trimester
01965	CPT	Anesthesia for incomplete or missed abortion procedures

Table D.4: Diagnosis and procedure codes used to identify terminations

Code	Code type	Description
635.00-635.92	ICD-9 diagnosis	Legally induced abortion, incomplete, complete, and unspecified
636.00-636.92	ICD-9 diagnosis	Illegally induced abortion, incomplete, complete, and unspecified
O04.5-O04.89	ICD-10 diagnosis	Induced termination of pregnancy
Z33.2	ICD-10 diagnosis	Encounter for elective termination of pregnancy
69.01	ICD-9 procedure	Dilation and curettage for termination of pregnancy
69.51	ICD-9 procedure	Aspiration curettage of uterus for termination of pregnancy
74.91	ICD-9 procedure	Hysterotomy to terminate pregnancy
75.0	ICD-9 procedure	Intra-amniotic injection for abortion
10A00ZZ-10A08ZZ	ICD-10 procedure	Abortion of Products of Conception
59840	CPT	Induced abortion by dilation and curettage
59841	CPT	Induced abortion by dilation and evacuation
59850	CPT	Induced abortion by one or more intra-amniotic injections
59851	CPT	Induced abortion by one or more intra-amniotic injections
59852	CPT	Induced abortion by one or more intra-amniotic injections
59855	CPT	Induced abortion one or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., luminaria)
59856	CPT	Induced abortion one or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., luminaria)
59857	CPT	Induced abortion one or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., luminaria)
01966	CPT	Anesthesia for induced abortion procedures

Table D.5: Diagnosis codes used to identify stillbirth

Code	Code type	Description
656.40-656.43	ICD-9 diagnosis	Intrauterine death, affecting management of mother
768.0-768.1	ICD-9 diagnosis	Fetal death from asphyxia or anoxia
V27.1	ICD-9 diagnosis	Outcome of delivery, single stillborn
V27.4	ICD-9 diagnosis	Outcome of delivery, twins, both stillborn
V27.7	ICD-9 diagnosis	Outcome of delivery, other multiple birth, all stillborn
O36.4XX0-O36.4XX9	ICD-10 diagnosis	Maternal care for intrauterine death
Z37.1	ICD-10 diagnosis	Single stillbirth
Z37.4	ICD-10 diagnosis	Twins, both stillborn
Z37.7	ICD-10 diagnosis	Other multiple births, all stillborn
P95	ICD-10 diagnosis	Stillbirth

Table D.6: Diagnosis codes used to identify live birth

Code	Code type	Description
650	ICD-9 diagnosis	Normal delivery
V27.0'	ICD-9 diagnosis	Outcome of delivery, single liveborn
V27.2'	ICD-9 diagnosis	Outcome of delivery, twins, both liveborn
V27.5'	ICD-9 diagnosis	Outcome of delivery, other multiple birth, all liveborn
V30.00-V30.2	ICD-9 diagnosis	Single liveborn
V31.00-V31.2	ICD-9 diagnosis	Twin birth, mate liveborn
V34.00-V34.2	ICD-9 diagnosis	Other multiple birth (three or more), mates all liveborn
V39.00-V39.2	ICD-9 diagnosis	Liveborn, unspecified whether single, twin or multiple
O80	ICD-10 diagnosis	Encounter for full-term uncomplicated delivery
O82	ICD-10 diagnosis	Encounter for cesarean delivery without indication
Z37.0	ICD-10 diagnosis	Single live birth
Z37.2	ICD-10 diagnosis	Twins, both liveborn
Z37.50-Z37.59	ICD-10 diagnosis	Multiple births, unspecified, all liveborn
Z38.00-Z38.7	ICD-10 diagnosis	Liveborn infants according to place of birth and type of delivery

Table D.7: Procedure codes used to identify delivery, unspecified outcome type

Code	Code type	Description
69.02	ICD-9	
69.52	ICD-9	
72.0-72.9	ICD-9	Forceps, Vacuum, And Breech Delivery
73.01-73.99	ICD-9	Other Procedures Inducing Or Assisting Delivery
74.0-74.4, 74.99	ICD-9	Cesarean Section
75.4	ICD-9	Manual removal of retained placenta
75.50-75.52	ICD-9	Repair Of Current Obstetric Laceration Of Uterus
75.61-75.69	ICD-9	Repair Of Other Current Obstetric Laceration
75.7	ICD-9	Manual exploration of uterine cavity, postpartum
75.8	ICD-9	Obstetric tamponade of uterus or vagina
75.91	ICD-9	Evacuation of obstetrical incisional hematoma of perineum
75.94	ICD-9	Immediate postpartum manual replacement of inverted uterus
0HQ9XZZ	ICD-10	Repair Perineum Skin, External Approach
0KQM0ZZ, 0KQM3ZZ, 0KQM4ZZ	ICD-10	Repair Perineum Muscle
0U7C7ZZ	ICD-10	Dilation of Cervix, Via Natural or Artificial Opening
0UQG0ZZ, 0UQG3ZZ, 0UQG4ZZ, 0UQG7ZZ, 0UQG8ZZ, 0UQGXZZ	ICD-10	Repair vagina
0W8NXZZ	ICD-10	Division of Female Perineum, External Approach
0WQN0ZZ, 0WQN3ZZ, 0WQN4ZZ, 0WQNXZZ	ICD-10	Repair Female Perineum
10D00Z0-10D00Z8	ICD-10	Extraction of Products of Conception
10D17Z9	ICD-10	Manual Extraction of Products of Conception, Retained, Via Natural or Artificial Opening
10D17ZZ	ICD-10	Extraction of Products of Conception, Retained, Via Natural or Artificial Opening
10D18Z9	ICD-10	Manual Extraction of Products of Conception, Retained, Via Natural or Artificial Opening Endoscopic
10D18ZZ	ICD-10	Extraction of Products of Conception, Retained, Via Natural or Artificial Opening Endoscopic
10E0XZZ	ICD-10	Delivery of Products of Conception, External Approach
3E033VJ	ICD-10	Introduction of Other Hormone into Peripheral Vein, Percutaneous Approach
3E0P7GC	ICD-10	Introduction of other therapeutic substance into female reproductive, via natural or artificial opening
59160	CPT	D/C following delivery
59400	CPT	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care
59409	CPT	Vaginal delivery only (with or without episiotomy and/or forceps)
59410	CPT	Vaginal delivery only (with or without episiotomy and/or forceps); including postpartum care
59414	CPT	Delivery of placenta , separate procedure
59510	CPT	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care
59514	CPT	Cesarean delivery only
59515	CPT	Cesarean delivery only; including postpartum care

Code	Code type	Description
59610	CPT	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care, after previous cesarean delivery
59612	CPT	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps)
59614	CPT	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps); including postpartum care
59618	CPT	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care, following attempted vaginal delivery after previous cesarean delivery
59620	CPT	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery
59622	CPT	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery; including postpartum care
59160	CPT	D/C following delivery
59400	CPT	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care
59409	CPT	Vaginal delivery only (with or without episiotomy and/or forceps)
59410	CPT	Vaginal delivery only (with or without episiotomy and/or forceps); including postpartum care
59414	CPT	Delivery of placenta , separate procedure
59618	CPT	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care, following attempted vaginal delivery after previous cesarean delivery
59620	CPT	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery
59622	CPT	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery; including postpartum care
59200	CPT	Insertion of cervical dilator (eg, laminaria, prostaglandin) (separate procedure)
59300	CPT	Episiotomy or vaginal repair, by other than attending
01968	CPT	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia (List separately in addition to code for primary procedure performed)
01969	CPT	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia (List separately in addition to code for primary procedure performed)
01963	CPT	Anesthesia for cesarean hysterectomy without any labor analgesia/anesthesia care
01962	CPT	Anesthesia for urgent hysterectomy following delivery
01967	CPT	Neuraxial labor analgesia/anesthesia for planned vaginal delivery (this includes any repeat subarachnoid needle placement and drug injection and/or any necessary replacement of an epidural catheter during labor)
01960	CPT	Anesthesia for vaginal delivery only
01961	CPT	Anesthesia for cesarean delivery only

Table D.8: Diagnosis and procedure codes used to identify ectopic and molar pregnancies

Code	Code type	Description
630	ICD-9 diagnosis	Hydatidform mole
631.8	ICD-9 diagnosis	Other abnormal products of conception
633.00-633.91	ICD-9 diagnosis	Ectopic pregnancy
O00.00-O00.91	ICD-10 diagnosis	Ectopic pregnancy
O01.0-O01.9	ICD-10 diagnosis	Hydatidiform mole
O02.0	ICD-10 diagnosis	Blighted ovum and nonhydatidiform mole
O02.89	ICD-10 diagnosis	Other abnormal products of conception
O02.9	ICD-10 diagnosis	Abnormal product of conception, unspecified
O08.1-O08.9	ICD-10 diagnosis	Complications following ectopic and molar pregnancy
66.62	ICD-9 procedure	Salpingectomy with removal of tubal pregnancy
74.3	ICD-9 procedure	Removal of extratubal ectopic pregnancy
10D27ZZ, 10D28ZZ	ICD-10 procedure	Extraction of Products of Conception, Ectopic
10T20ZZ, 10T24ZZ	ICD-10 procedure	Resection of Products of Conception, Ectopic
59120	CPT	Surgical treatment of ectopic pregnancy; tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach
59121	CPT	Surgical treatment of ectopic pregnancy; tubal or ovarian, without salpingectomy and/or oophorectomy
59130	CPT	Surgical treatment of ectopic pregnancy; abdominal pregnancy
59135	CPT	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy
59136	CPT	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus
59140	CPT	Surgical treatment of ectopic pregnancy; cervical, with evacuation
59150	CPT	Laparoscopic treatment of ectopic pregnancy; without salpingectomy and/or oophorectomy
59151	CPT	Laparoscopic treatment of ectopic pregnancy; with salpingectomy and/or oophorectomy
59870	CPT	Uterine evacuation and curettage for hydatidiform mole
59100	CPT	Hysterotomy, abdominal (eg, for hydatidiform mole, abortion)

Table D.9: Diagnosis codes used to define comorbidities

Comorbidities	ICD-9 diagnosis codes	ICD-10 diagnosis codes	CPT codes
Asthma	493.XX	J45.XXX	
Renal disease	581.XX, 582.XX, 583.XX, 585.XX, 587, 588.XX, 646.2X	N03.X, N04.X, N05.X, N18.X, N25.X, N26.9	
Depression	296.XX, 311	F31.XX, F32.XX, F33.XX	
Other mental health disorders	290.XX, 293.XX, 294.XX, 295.XX, 297.X, 298.X, 299.XX, 300.XX, 301.XX, 302.XX, 306.XX, 307.XX, 308.XX, 309.XX, 310.XX, 312.XX, 313.XX, 314.X, 315.XX	F01.X, F02.X, F03.X, F04, F05, F06.XX, F07.XX, F09, F20.XX, F21, F22, F23, F24, F25.X, F28, F29, F30.XX, F34.XX, F39, F40.XX, F41.X, F42.X, F43.XX, F44.XX, F45.XX, F48.X, F60.XX, F63.XX	
Hypertension	401.X, 402.XX, 403.XX, 404.XX, 405.XX	I10, I11.X, I12.X, I13.XX, I15.X, I16.X	
Sleep disorders	307.4X, 347.XX, 780.5X	F51.XX, G47.0X, G47.1X, G47.2X, G47.3X, G47.4X	
Diabetes	250.XX, 648.0X	E08.XXX, E10.XXX, E11.XXX, E13.XXX, O24.0XX, O24.1XX, O24.3XX, O24.8XX, O24.9XX	
Seizure disorders	333.2, 345.XX, 345.6X, 780.3X	G25.3, G40.XXX, R56.XX	
Alcohol abuse	291.XX, 303.XX, 305.0X	F10.XXX, O35.4XXX, O99.3XXX	
Drug abuse	292.XX, 304.XX, 305.XX, 648.3X, 655.5X	F11.XXX, F12.XXX, F13.XXX, F14.XXX, F15.XXX, F16.XXX, F18.XXX, F19.XXX, O35.XXXX, O99.XXX	
High risk pregnancy	V23.XX	O09.XXX	
Nausea and vomiting of pregnancy	643.XX	O21.X	
Nausea and vomiting	787.0X	R11.XX	
Hyperemesis gravidarum	643.0X, 643.1X	O21.0, O21.1	
Chemotherapy or radiation therapy	909.2, 990, V58.0, V58.11, V58.12, V67.2	E93.31, T45.1X5A, T45.1X5S, T45.95XA, Z08, Z51.11, Z51.12	96401, 96402, 96405, 96406, 96409, 96411, 96413, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96440, 96446, 96450
Surgical procedure	995.22	T41.0X5A, T41.1X5A, T41.205A, T41.295A, T41.45XA, T88.59XA	10000-36000, 36598-69990

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