ORIGINAL ARTICLE

Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes

Björn Pasternak, M.D., Ph.D., Henrik Svanström, M.Sc., and Anders Hviid, Dr.Med.Sci.

ABSTRACT

BACKGROUND

Ondansetron is frequently used to treat nausea and vomiting during pregnancy, but the safety of this drug for the fetus has not been well studied.

METHODS

We investigated the risk of adverse fetal outcomes associated with ondansetron administered during pregnancy. From a historical cohort of 608,385 pregnancies in Denmark, women who were exposed to ondansetron and those who were not exposed were included, in a 1:4 ratio, in propensity-score–matched analyses of spontaneous abortion (1849 exposed women vs. 7396 unexposed women), stillbirth (1915 vs. 7660), any major birth defect (1233 vs. 4932), preterm delivery (1792 vs. 7168), and birth of infants at low birth weight and small for gestational age (1784 vs. 7136). In addition, estimates were adjusted for hospitalization for nausea and vomiting during pregnancy (as a proxy for severity) and the use of other antiemetics.

RESULTS

Receipt of ondansetron was not associated with a significantly increased risk of spontaneous abortion, which occurred in 1.1% of exposed women and 3.7% of unexposed women during gestational weeks 7 to 12 (hazard ratio, 0.49; 95% confidence interval [CI], 0.27 to 0.91) and in 1.0% and 2.1%, respectively, during weeks 13 to 22 (hazard ratio, 0.60; 95% CI, 0.29 to 1.21). Ondansetron also conferred no significantly increased risk of stillbirth (0.3% for exposed women and 0.4% for unexposed women; hazard ratio, 0.42; 95% CI, 0.10 to 1.73), any major birth defect (2.9% and 2.9%, respectively; prevalence odds ratio, 1.12; 95% CI, 0.69 to 1.82), preterm delivery (6.2% and 5.2%; prevalence odds ratio, 0.90; 95% CI, 0.66 to 1.25), delivery of a low-birth-weight infant (4.1% and 3.7%; prevalence odds ratio, 0.76; 95% CI, 0.51 to 1.13), or delivery of a small-for-gestational-age infant (10.4% and 9.2%; prevalence odds ratio, 1.13; 95% CI, 0.89 to 1.44).

CONCLUSIONS

Ondansetron taken during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes. (Funded by the Danish Medical Research Council.)

From the Department of Epidemiology Research, Statens Serum Institut, Copenhagen. Address reprint requests to Dr. Pasternak at the Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark, or at bjp@ssi.dk.

This article was updated on February 28, 2013, at NEJM.org.

N Engl J Med 2013;368:814-23.
DOI: 10.1056/NEJMoa1211035

Nausea and vomiting are common during pregnancy, affecting more than half of all pregnant women.[1,2] Whereas these symptoms can be managed conservatively in most pregnant women, 10 to 15% receive drug treatment.[1,3] Because nausea and vomiting manifest in early pregnancy, with onset between 3 and 8 weeks of gestation and with peak symptoms in weeks 7 to 12 in most cases,[1,2,4] drug treatment often coincides with the period during which the fetus is most susceptible to teratogenic effects.

Among the drugs available for the treatment of nausea and vomiting during pregnancy,[1] the 5-hydroxytryptamine type 3 receptor antagonist ondansetron has become the most frequently used prescription antiemetic in the United States.[5] Between 2004 and 2008, almost 3% of women who were enrolled in the Slone Epidemiology Center Birth Defects Study reported having received ondansetron during the first trimester; ondansetron was the fifth most frequently used prescription medication overall.[5] Despite the prevalent use of this drug during pregnancy, data that support its safety for the fetus are limited. A cohort study showed no significant differences in pregnancy and fetal outcomes between 176 women who were exposed to ondansetron and 352 who were not exposed.[6] A case–control study showed that the use of ondansetron was associated with an increased risk of cleft palate but not of cleft lip, hypospadias, or neural-tube defects.[3]

Using Danish registries, we conducted a historical cohort study to investigate whether receipt of ondansetron during pregnancy was associated with an increased risk of adverse fetal outcomes, defined as spontaneous abortion, stillbirth, any major birth defect, preterm delivery, low birth weight, and small size for gestational age.

METHODS

STUDY COHORT

Using information from the Medical Birth Registry[7] and the National Patient Register[8] in Denmark, we established a nationwide historical cohort of all pregnancies that resulted in a singleton live birth or stillbirth or ended with any abortive outcome in the period from January 1, 2004, through March 31, 2011. Before this study period, ondansetron was rarely used during pregnancy. The sources of data for this study, which also included the National Prescription Registry,[9] the Central Person Register,[10] and Statistics Denmark, are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Pregnancy onset was defined as the first day of the last menstrual period and was estimated by subtracting the gestational age from the date of birth or abortive outcome. We excluded pregnancies for which information on gestational age was missing or implausible and pregnancies with multiple records on overlapping dates. For the analyses of spontaneous abortion and stillbirth, we also excluded women in whom abortions occurred at a gestational age of less than 6 completed weeks (since many early pregnancy losses are not recognized clinically and thus these outcomes would have been subject to misclassification) and women who were exposed to ondansetron within the first 6 weeks of gestation. For analyses involving birth weight, pregnancies with missing information on birth weight were excluded. The study was approved by the Danish Data Protection Agency. In Denmark, ethics approval and informed consent are not required for registry-based research.

ONDANSETRON EXPOSURE

We used information from the National Prescription Registry to identify prescriptions for ondansetron dispensed to women in the cohort. No woman had used any other 5-hydroxytryptamine type 3 receptor antagonist. We defined specific exposure time windows for the respective analyses: the first trimester (through 12 gestational weeks) for any major birth defect, any time before 37 completed weeks for preterm delivery, any time during pregnancy for analyses involving birth weight, week 7 through week 22 for spontaneous abortion, and week 7 until birth for stillbirth. The timing of exposure was defined by the date the prescription was filled. In each analysis, women who did not receive ondansetron throughout the exposure time window were categorized as "unexposed." Those who had filled ondansetron prescriptions within 1 month before pregnancy onset were excluded.

OUTCOMES

The National Patient Register was used to identify cases of major birth defects (1-year follow-up after birth) and spontaneous abortion (fetal loss

through 22 gestational weeks). Validation studies of the National Patient Register showed that registrations were correct for 99% of the diagnoses of spontaneous abortion and 88% of the diagnoses of birth defects.[11,12] Major birth defects were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification,[13] with some modifications, including the exclusion of infants with chromosomal aberrations (e.g., Down's syndrome) and those with known causes of birth defects (e.g., fetal alcohol syndrome) (see the Supplementary Appendix). Cases of preterm delivery (delivery before 37 completed weeks), infants born small for gestational age (lowest 10th percentile of the gestational age–specific birth weight within the cohort), infants born at low birth weight (<2500 g), and stillbirth (fetal loss after 22 completed weeks) were ascertained on the basis of data from the Medical Birth Registry.

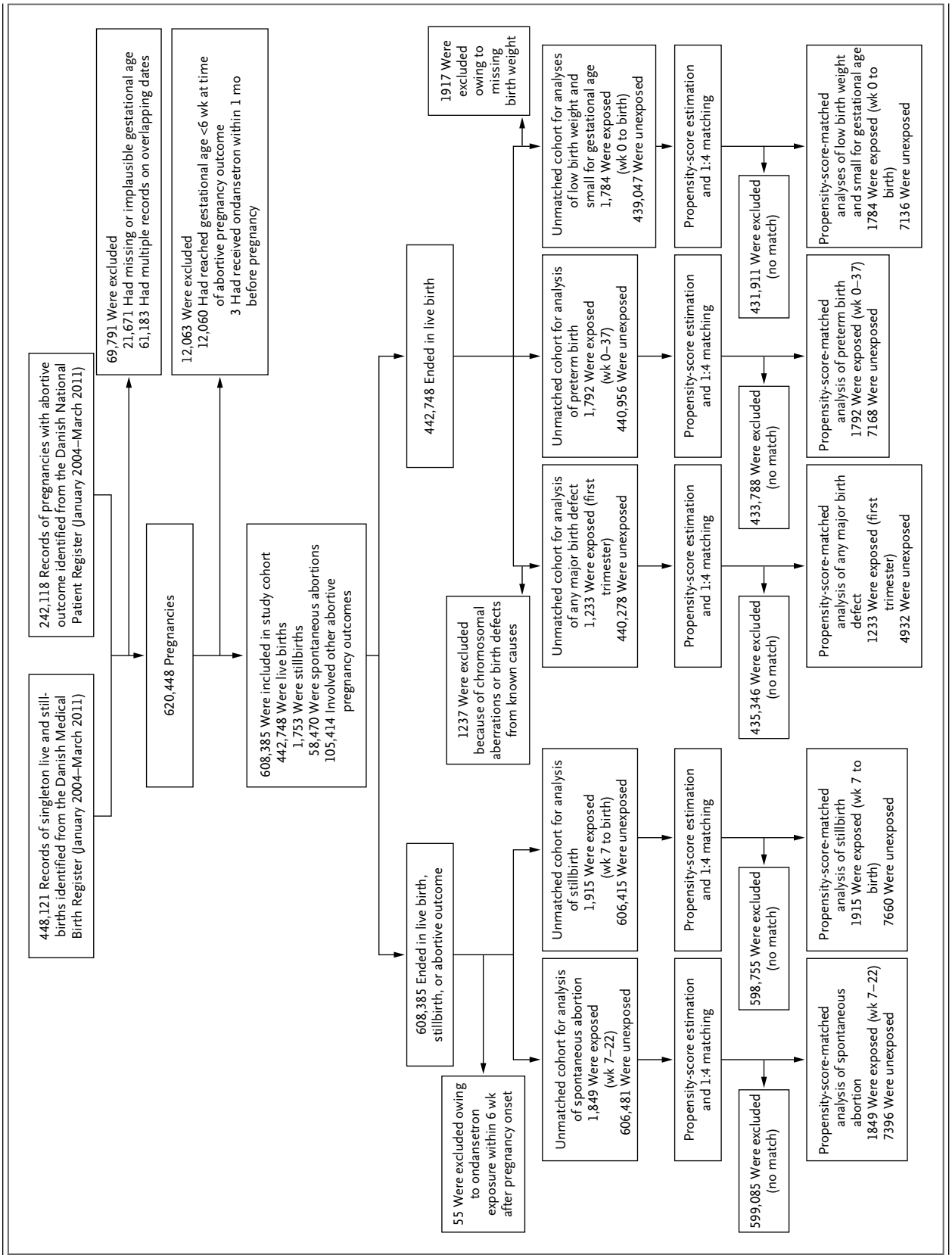
STATISTICAL ANALYSIS

For analyses of spontaneous abortion and stillbirth, which were based on all pregnancies in the cohort (live births, stillbirths, and abortive outcomes), we used Cox proportional-hazards regression models to estimate hazard ratios for the comparison of pregnancies in which women were and were not exposed to ondansetron. The gestational age at which events occurred was taken into account by using the gestational age in days as the time scale in the Cox model. For the analysis of spontaneous abortion, follow-up (gestational weeks 7 to 22) was censored if an abortive outcome other than spontaneous abortion (e.g., induced abortion) occurred. For the analysis of stillbirth, follow-up (gestational week 7 to birth) was censored if any abortive outcome occurred. The proportional-hazards assumption was assessed by measuring the interaction between treatment status and the time scale by means of the Wald test. The analyses of birth defects, preterm delivery, and birth weight were based on live births; logistic regression was used to estimate prevalence odds ratios.

To account for potential confounders, we used logistic regression to estimate propensity scores as the probability of exposure to ondansetron given baseline characteristics at pregnancy onset (details on included covariates are provided in Table S2 in the Supplementary Appendix); all two-way interactions between demographic variables were included in the scores. Variables with missing values (Table S3 in the Supplementary Appendix) were imputed with the use of the mode. After estimation of a distinct propensity score for each exposure time window, women who had been exposed to ondansetron were matched, in a 1:4 ratio, to unexposed women in accordance with the nearest-neighbor–matching algorithm (a caliper width equal to 0.1 of the standard deviation of the logit score was used).[14,15] Because the risk of fetal loss is highly dependent on gestational age, we also used gestational age as a matching criterion for the analyses of spontaneous abortion and stillbirth — that is, on the basis of the gestational age at exposure (index date) for each woman exposed to ondansetron. Women who were not exposed and who had survived through this index date were eligible as matches. Finally, all models were adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting (as a proxy measure of severity) and exposure to antiemetics other than ondansetron during pregnancy.

Figure 1 (facing page). Study Design.
For propensity-score–matched analyses, women who were exposed to ondansetron and those who were not exposed were included in a 1:4 ratio. For the 69,791 records initially excluded, some were excluded in both categories.

In preplanned sensitivity analyses, we restricted the definition of exposure in the analysis of birth defects to the period of maximal susceptibility to teratogenic agents (gestational weeks 4 to 10, or 2 to 8 weeks after the estimated time of conception).[16] In addition, we reanalyzed the birth-defect outcome, also including birth defects detected among induced abortions and stillbirths (details are provided in the Supplementary Appendix). Because nausea and vomiting are associated with a decreased risk of spontaneous abortion[17,18] (with the potential to introduce confounding by indication), we analyzed the risk of spontaneous abortion by comparing exposure to ondansetron with exposure to antiemetic antihistamines considered safe in pregnancy (promethazine, cyclizine, or meclizine)[1,19] (using a 1:1 ratio in a propensity-score–matched analysis). We also modeled the effect of adjusting for an unmeasured protective confounder at different levels of prevalence and different strengths of association with birth defects, using the array approach described by



Schneeweiss.[20] Insofar as women who refill a prescription are more likely to have used the medication, we also conducted post hoc analyses categorizing women according to whether they filled one prescription or two or more prescriptions. SAS software (version 9.2) was used for the statistical analysis.

RESULTS

STUDY POPULATION

Figure 1 shows the study design and the inclusion of pregnancies in the analyses of each specific outcome. After exclusions, the study cohort comprised 608,385 pregnancies. Exposure to ondansetron occurred in 1970 (0.3%) of these pregnancies; the first prescription was filled at a median of 70 gestational days (i.e., 10 weeks; interquartile range, 57 to 88 days). The median number of doses was 10 per prescription (interquartile range, 10 to 10) and 30 per pregnancy (interquartile range, 10 to 65).

Tables S4 and S5 in the Supplementary Appendix show participants' characteristics before propensity-score matching. In unadjusted analyses conducted before propensity-score matching, the risk of spontaneous abortion was significantly decreased among women who were exposed to ondansetron, as compared with unexposed women (Table S6 in the Supplementary Appendix). There was no increased risk of stillbirth, any major birth defect, infant born at low birth weight, or infant born at small size for gestational age associated with ondansetron exposure, whereas the risk of preterm delivery was significantly increased (Table S6 in the Supplementary Appendix).

PROPENSITY-SCORE–MATCHED ANALYSES

For the propensity-score–matched analyses of spontaneous abortion and stillbirth, which were based on all pregnancies, 1849 women who were exposed to ondansetron between 7 and 22 gestational weeks and 1915 women who were exposed

Table 1. Characteristics of Women Included in the Propensity-Score–Matched Analysis, According to Ondansetron Exposure during Pregnancy.*

Variable	Any Major Birth Defect		Spontaneous Abortion		Low Birth Weight and Small for Gestational Age	
	Unexposed in First Trimester (N=4932)	Exposed in First Trimester (N=1233)	Unexposed at 7 to 22 Wk (N=7396)	Exposed at 7 to 22 Wk (N=1849)	Unexposed from 0 Wk to Birth (N=7136)	Exposed from 0 Wk to Birth (N=1784)
Age at pregnancy onset — yr	30±4.7	30±4.7	30±5.0	30±4.9	30±4.8	30±4.8
Married or living with partner — no. (%)	4260 (86.4)	1065 (86.4)	6386 (86.3)	1565 (84.6)	6167 (86.4)	1538 (86.2)
Bachelor's degree or higher educational level — no. (%)	1509 (30.6)	376 (30.5)	2246 (30.4)	553 (29.9)	2185 (30.6)	536 (30.0)
Gross household income in 3rd quintile — no. (%)†	1187 (24.1)	281 (22.8)	1815 (24.5)	433 (23.4)	1794 (25.1)	422 (23.7)
Parity — no. (%)						
1	2295 (46.5)	535 (43.4)	3130 (42.3)	751 (40.6)	3044 (42.7)	744 (41.7)
2	717 (14.5)	183 (14.8)	1032 (14.0)	277 (15.0)	976 (13.7)	248 (13.9)
≥3	296 (6.0)	79 (6.4)	367 (5.0)	104 (5.6)	376 (5.3)	99 (5.5)
Same outcome in previous pregnancy — no. (%)	313 (6.3)	88 (7.1)	1362 (18.4)	335 (18.1)	643 (9.0)‡	175 (9.8)‡
Smoking during pregnancy — no. (%)	285 (5.8)	74 (6.0)	NA	NA	463 (6.5)	128 (7.2)
Body-mass index before pregnancy — no. (%)§						
<18.5	175 (3.5)	45 (3.6)	NA	NA	275 (3.9)	67 (3.8)
18.5–24.9	3199 (64.9)	783 (63.5)	NA	NA	4432 (62.1)	1097 (61.5)
25.0–29.9	985 (20.0)	265 (21.5)	NA	NA	1527 (21.4)	383 (21.5)
30.0–34.9	432 (8.8)	98 (7.9)	NA	NA	632 (8.9)	161 (9.0)
≥35.0	141 (2.9)	42 (3.4)	NA	NA	270 (3.8)	76 (4.3)
Medical history — no. (%)						
Diabetes mellitus	70 (1.4)	26 (2.1)	115 (1.6)	39 (2.1)	102 (1.4)	36 (2.0)
Cancer diagnosed in past 6 mo	3 (0.1)	1 (0.1)	2 (<0.1)	1 (0.1)	4 (0.1)	1 (0.1)

Table 1. (Continued.)

Variable	Any Major Birth Defect		Spontaneous Abortion		Low Birth Weight and Small for Gestational Age	
	Unexposed in First Trimester (N=4932)	Exposed in First Trimester (N=1233)	Unexposed at 7 to 22 Wk (N=7396)	Exposed at 7 to 22 Wk (N=1849)	Unexposed from 0 Wk to Birth (N=7136)	Exposed from 0 Wk to Birth (N=1784)
Medications — no. (%)						
PPI or H_2 blocker in past 3 mo	147 (3.0)	41 (3.3)	1778 (2.4)	60 (3.2)	209 (2.9)	59 (3.3)
NSAID in past 3 mo	383 (7.8)	107 (8.7)	618 (8.4)	165 (8.9)	585 (8.2)	149 (8.4)
Antimigraine drug in past 3 mo	179 (3.6)	38 (3.1)	180 (2.4)	48 (2.6)	200 (2.8)	48 (2.7)
In vitro fertilization drug in past 3 mo	249 (5.0)	70 (5.7)	393 (5.3)	99 (5.4)	348 (4.9)	101 (5.7)
No. of prescription drugs in past 6 mo						
1–2	1988 (40.3)	484 (39.3)	2956 (40.0)	723 (39.1)	2897 (40.6)	711 (39.9)
3–4	1012 (20.5)	257 (20.8)	1569 (21.2)	401 (21.7)	1485 (20.8)	380 (21.3)
≥5	680 (13.6)	183 (14.8)	1053 (14.2)	281 (15.2)	1022 (14.3)	266 (14.9)
Hospital admission for hyperemesis or nausea and vomiting — no. (%)¶	36 (0.7)	627 (50.9)	68 (0.9)	959 (51.9)	112 (1.6)	1004 (56.3)
Treatment with antiemetic other than ondansetron¶‖	209 (4.2)	500 (40.6)	349 (4.7)	800 (43.3)	430 (6.0)	775 (43.4)

* Plus–minus values are means SD. Each pregnancy with ondansetron exposure was matched to four pregnancies without exposure on the basis of the propensity score. The characteristics shown were current at the time of pregnancy onset, unless stated otherwise; socioeconomic variables were current at the start of the year of pregnancy onset. There were no significant differences in the distribution of characteristics between the matched exposed and unexposed groups, apart from the use of a PPI (proton-pump inhibitor) or H_2 blocker (histamine-2–receptor blocker) among women included in the analysis of spontaneous abortion ($P<0.05$) and the use of a PPI or H_2 blocker among women included in the analysis of stillbirth ($P<0.05$). Percentages may not total 100 because of rounding. For additional information, see Tables S7 and S8 in the Supplementary Appendix. NA denotes not available, and NSAID nonsteroidal antiinflammatory drug.

† The range of the third quintile for income was approximately $72,000 to $110,700 (about 400,000 to 615,000 Danish kroner).

‡ These numbers refer only to previous pregnancies in which infants were small for gestational age.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ This variable was not included in the propensity score. Hospitalization and treatment with antiemetics occurred within the respective exposure time window.

‖ Other antiemetics were metoclopramide, antihistamines, scopolamine, and domperidone.

between week 7 and birth were matched in a ratio of 1:4 to unexposed pregnant women (Fig. 1). For the propensity-score–matched analyses of birth defects, preterm delivery, infants born small for gestational age, and infants with low birth weight, which were based on live births, 1233 women who were exposed in the first trimester, 1792 who were exposed before 37 completed gestational weeks, and 1784 who were exposed at any time during pregnancy were matched in a 1:4 ratio with unexposed women. For all analyses, the matched groups were well balanced with regard to baseline characteristics (Table 1, and Tables S7 and S8 in the Supplementary Appendix). Among women who were exposed to ondansetron, more than 50% were hospitalized for hyperemesis or nausea and vomiting during pregnancy and almost half received another antiemetic (Table 1).

Table 2 shows the propensity-score–matched analyses of adverse fetal outcomes associated with exposure to ondansetron in pregnancy, with and without adjustment for hospitalization for hyperemesis or nausea and vomiting and the use of other antiemetics. Because the proportional-hazards assumption was not fulfilled in the planned analysis of spontaneous abortion (follow-up, 7 to 22 gestational weeks; $P=0.02$ for the interaction between treatment status and gestational age), the follow-up period was divided into two strata: 7 to 12 weeks and 13 to 22 weeks. This analysis included a total of 354 cases, with 215 cases occurring in weeks 7 to 12 and 139 cases in weeks 13 to 22. Pregnant women who were exposed to ondansetron were not at increased risk for spontaneous abortion, as compared with unexposed women, with an adjusted hazard ratio of 0.49 (95% confidence interval [CI], 0.27 to 0.91) in weeks 7 to 12 and of 0.60 (95% CI, 0.29 to 1.21) in weeks 13 to 22. The analysis of stillbirth included 6 cases among 1915 women who

Table 2. Propensity-Score–Matched Analyses of Adverse Fetal Outcomes Associated with Ondansetron Exposure in Pregnancy.*

Outcome	Exposed	Unexposed	Measure of Association† (95% CI)	
			Unadjusted	Adjusted
	no. with outcome/total no. (%)			
Spontaneous abortion (gestational wk)				
7–12	15/1345 (1.1)	200/5380 (3.7)	0.30 (0.18–0.51)	0.49 (0.27–0.91)
13–22	17/1739 (1.0)	122/6889 (1.8)	0.55 (0.33–0.91)	0.60 (0.29–1.21)
Stillbirth	6/1915 (0.3)	27/7660 (0.4)	0.90 (0.37–2.19)	0.42 (0.10–1.73)
Any major birth defect	36/1233 (2.9)	141/4932 (2.9)	1.02 (0.70–1.48)	1.12 (0.69–1.82)
Preterm delivery	111/1792 (6.2)	374/7168 (5.2)	1.20 (0.96–1.49)	0.90 (0.66–1.25)
Low birth weight	73/1784 (4.1)	265/7136 (3.7)	1.11 (0.85–1.44)	0.76 (0.51–1.13)
Small for gestational age	185/1784 (10.4)	656/7136 (9.2)	1.14 (0.96–1.36)	1.13 (0.89–1.44)

* All measures of association are from propensity-score–matched analyses that included women who were exposed to ondansetron and those who were not exposed in a 1:4 ratio. Measures of association were adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting and exposure to antiemetics other than ondansetron within the respective exposure time window. Spontaneous abortion was defined as fetal loss between 7 and 22 weeks of gestation and stillbirth as fetal loss after 22 weeks of gestation. The category of major birth defects did not include infants with chromosomal abnormalities (e.g., Down's syndrome) and those with known causes (e.g., fetal alcohol syndrome). Preterm delivery was defined as delivery before 37 completed gestational weeks, low birth weight as less than 2500 g, and infant born small for gestational age as the lowest 10th percentile of the gestational age–specific birth weight within the cohort.

† For the outcomes of spontaneous abortion and stillbirth, the reported measures of association are hazard ratios; for all other outcomes, the reported measures of association are prevalence odds ratios.

were exposed to ondansetron (0.3%) and 27 cases among 7660 women who were not exposed (0.4%) (adjusted hazard ratio, 0.42; 95% CI, 0.10 to 1.73).

Among 1233 women who were exposed to ondansetron in the first trimester (first prescription at a median of 63 gestational days; interquartile range, 54 to 73), 36 infants (2.9%) were registered as having a major birth defect during the first year of life, as compared with 141 of 4932 infants (2.9%) born to women who were not exposed (adjusted prevalence odds ratio, 1.12; 95% CI, 0.69 to 1.82). The specific birth defects among infants who were and were not exposed to ondansetron are listed in Table S9 in the Supplementary Appendix; there were no cases of cleft palate in the group exposed to ondansetron.

Among 1792 women who were exposed to ondansetron before 37 completed weeks of gestation, there were 111 preterm deliveries (6.2%), as compared with 374 among 7168 women who were not exposed (5.2%) (adjusted prevalence odds ratio, 0.90; 95% CI, 0.66 to 1.25). Exposure to ondansetron at any time during pregnancy was not associated with infants born with low birth weight (4.1% among infants who had been exposed to ondansetron and 3.7% among those who had not been exposed; adjusted prevalence odds ratio, 0.76; 95% CI, 0.51 to 1.13) or with infants who were small for gestational age at birth (10.4% among exposed infants and 9.2% among unexposed infants; adjusted prevalence odds ratio, 1.13; 95% CI, 0.89 to 1.44).

SENSITIVITY ANALYSES

The adjusted prevalence odds ratio for any major birth defect was similar to that in the primary analysis in sensitivity analyses in which the exposure time window was restricted to the period of maximal susceptibility to teratogenic agents (gestational weeks 4 to 10) and including birth defects among induced abortions and stillbirths (Table 3). As compared with pregnancies in which there was exposure to antihistamine antiemetics, those in which there was exposure to ondansetron were at no significantly different risk of spontaneous abortion (Table 3). The estimates for adverse fetal outcomes were similar between women who filled one ondansetron prescription and those who filled two or more prescriptions (Table 3).

Table 3. Sensitivity Analyses of Ondansetron Exposure in Pregnancy and Adverse Fetal Outcomes.*

Outcome	Adverse Fetal Outcomes	Measure of Association (95% CI)†	
		Unadjusted	Adjusted
	no. with outcome/total no. (%)		
Any major birth defect, ondansetron exposure in gestational wk 4–10			
Ondansetron	25/820 (3.0)	1.07 (0.69–1.65)	1.34 (0.80–2.26)
Unexposed	141/4932 (2.9)	1.00	1.00
Any major birth defect, cases from induced abortions and stillbirths included			
Ondansetron	38/1241 (3.1)	0.95 (0.66–1.36)	1.12 (0.70–1.77)
Unexposed	160/4964 (3.2)	1.00	1.00
Spontaneous abortion, ondansetron vs. antiemetic antihistamine			
Ondansetron	19/1192 (1.6)	0.68 (0.38–1.22)	0.72 (0.38–1.34)
Antihistamine	29/1192 (2.4)	1.00	1.00
All adverse outcomes, according to no. of filled prescriptions for ondansetron			
Spontaneous abortion			
1 prescription	22/1812 (1.2)	0.51 (0.33–0.79)	0.68 (0.41–1.13)
≥2 prescriptions	10/1164 (0.9)	0.27 (0.14–0.50)	0.36 (0.18–0.72)
Unexposed	322/9245 (3.5)	1.00	1.00
Stillbirth			
1 prescription	3/1876 (0.2)	1.31 (0.40–4.31)	0.64 (0.13–3.07)
≥2 prescriptions	3/1196 (0.3)	0.69 (0.21–2.28)	0.30 (0.06–1.53)
Unexposed	27/7660 (0.4)	1.00	1.00
Any major birth defect			
1 prescription	14/368 (3.8)	1.34 (0.77–2.35)	1.41 (0.75–2.62)
≥2 prescriptions	22/865 (2.5)	0.89 (0.56–1.40)	0.98 (0.56–1.72)
Unexposed	141/4932 (2.9)	1.00	1.00
Preterm delivery			
1 prescription	35/627 (5.6)	1.07 (0.75–1.53)	0.85 (0.56–1.28)
≥2 prescriptions	76/1165 (6.5)	1.27 (0.98–1.64)	0.94 (0.66–1.35)
Unexposed	374/7168 (5.2)	1.00	1.00
Low birth weight			
1 prescription	24/625 (3.8)	1.04 (0.68–1.59)	0.75 (0.46–1.24)
≥2 prescriptions	49/1159 (4.2)	1.14 (0.84–1.56)	0.77 (0.49–1.19)
Unexposed	265/7136 (3.7)	1.00	1.00
Small for gestational age			
1 prescription	65/625 (10.4)	1.15 (0.88–1.50)	1.14 (0.84–1.54)
≥2 prescriptions	120/1159 (10.4)	1.14 (0.93–1.40)	1.13 (0.86–1.49)
Unexposed	656/7136 (9.2)	1.00	1.00

* Baseline characteristics of pregnancies in the analysis of birth defects in which induced abortions and stillbirths were included and in the analysis of spontaneous abortion in which exposure to ondansetron was compared with exposure to an antiemetic antihistamine are shown in Tables S9 and S10 in the Supplementary Appendix, respectively. In women who were exposed to ondansetron and who had induced abortions or stillbirths, there were 36 infants with birth defects among 1233 live births, 0 cases among 3 stillbirths, and 2 cases among 5 induced abortions.

† For the outcomes of spontaneous abortion and stillbirth, the reported measures of association are hazard ratios; for all other outcomes, the reported measures of association are prevalence odds ratios. Measures of association were adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting and for exposure to antiemetics other than ondansetron within the respective exposure time window, apart from the hazard ratio for spontaneous abortion in the analysis of ondansetron versus antiemetic antihistamine, which was adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting.

Because no increased risk of birth defects was detected in association with ondansetron exposure, we modeled the effect of a hypothetical unmeasured confounder that might mask a true risk and found that its influence on the observed estimate would be relatively small (Table S12 in the Supplementary Appendix). For instance, if a confounder halved the risk of birth defects and was twice as prevalent in the group exposed to ondansetron, the observed estimate of 1.12 would have been biased by 11.1% and the confounder-adjusted estimate would be 1.26.

DISCUSSION

In this nationwide cohort study in Denmark, ondansetron exposure in pregnancy was not associated with a significantly increased risk of major adverse fetal outcomes. On the basis of the upper limits of the confidence intervals for the risk estimates, our findings are inconsistent with increases in risk associated with ondansetron of more than 25% for preterm delivery, 44% for infants who were small for gestational age at birth, and 82% for any major birth defect, among others.

A potential source of confounding in observational studies of medication effects is that the condition for which the treatment is used may itself be associated with the study outcome (i.e., confounding by indication). Our findings that pregnant women who were exposed to ondansetron were at a significantly lower risk for spontaneous abortion as compared with unexposed women, but at a similar risk as compared with women exposed to an antihistamine, support the conclusions that nausea and vomiting, rather than the treatment of these conditions with ondansetron, are associated with a lower risk of spontaneous abortion. Several previous studies have reported inverse associations between nausea and vomiting in pregnancy and spontaneous abortion of similar magnitude as the associations between ondansetron and spontaneous abortion in our study.[17,18] Therefore, the data do not indicate that any protective effects should be attributed to ondansetron; rather, these data provide reassurance that the drug was not associated with an increased risk of spontaneous abortion.

An important question is whether some unmeasured confounder may have masked a true risk associated with ondansetron. For instance, data on folic acid supplementation were not available for our analysis of birth defects. To address this problem, we modeled the effect of an unmeasured confounder and found that even if the difference in confounder prevalence between the women who were and were not exposed to ondansetron had been large and the protective association with the outcome very strong, the confounder-adjusted estimate would have been relatively close to the observed estimate. Women who are exposed to ondansetron are much more likely to have nausea and vomiting than women who are not exposed to this medication. We adjusted our analyses for hospitalization for nausea and vomiting (as a proxy for severity), but data were not available on nausea and vomiting that did not require hospitalization.

In the majority of pregnancies with exposure to ondansetron that were included in the analysis of birth defects, the exposure occurred in the second half of the first trimester. Although this pattern of exposure probably reflects the fact that nausea and vomiting peak during this period,[1,2,4] it also implies that the results of the birth-defect analysis primarily apply to the second half of the first trimester.

Although the prescription of ondansetron for pregnant women has increased considerably,[5] we are aware of only two controlled studies that have assessed its fetal safety. A cohort study from Canadian and Australian teratology information services reported no significant differences in the frequencies of miscarriage, stillbirth, induced abortion, major malformations, mean birth weight, or mean gestational age between 176 pregnant women who were exposed to ondansetron and 352 women who were not exposed.[6] A case–control analysis from the National Birth Defects Prevention Study revealed that the use of ondansetron was associated with a significant increase in the risk of cleft palate but not of cleft lip, hypospadias, or neural-tube defects.[3] Our findings are consistent with those from the cohort study. Because we analyzed birth defects in aggregate, our results cannot be directly compared with those from the case–control study. We identified no cases of cleft palate among 1233 infants exposed to ondansetron in the first trimester, but our study was not powered to assess the risks of individual defects; this question needs to be addressed in future, adequately powered studies. Our study expands

the available data on ondansetron safety in pregnancy by including a large number of exposed pregnancies, investigating major adverse outcomes, considering the effects of exposure throughout pregnancy, and modeling comparative risk estimates while controlling for potential confounders.

In conclusion, in this registry-based cohort study, we found that exposure to ondansetron in pregnancy was not associated with a significant increase in the risk of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or born small for gestational age. Although these results cannot definitively rule out the possibility of adverse effects in association with ondansetron, the results do provide reassurance regarding the use of this agent for nausea and vomiting in pregnancy.

Supported by a grant from the Danish Medical Research Council (11-115854, to Dr. Pasternak).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Niebyl JR. Nausea and vomiting in pregnancy. N Engl J Med 2010;363:1544-50.
2. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 2000;182:931-7.
3. Anderka M, Mitchell AA, Louik C, Werler MM, Hernández-Diaz S, Rasmussen SA. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res A Clin Mol Teratol 2012;94:22-30.
4. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43:245-8. [Erratum, Br J Gen Pract 1993;43:325.]
5. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol 2011; 205:51-8.
6. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004;111:940-3.
7. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45:320-3.
8. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:Suppl:30-3.
9. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:Suppl: 38-41.
10. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. Dan Med Bull 2006;53:441-9.
11. Larsen H, Nielsen GL, Bendsen J, Flint C, Olsen J, Sørensen HT. Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. Scand J Public Health 2003;31:12-6.
12. Lohse SR, Farkas DK, Lohse N, et al. Validation of spontaneous abortion diagnoses in the Danish National Registry of Patients. Clin Epidemiol 2010;2:247-50.
13. Coding of Eurocat subgroups of congenital anomalies (version 2012). In: European Surveillance of Congenital Anomalies (Eurocat) guide 1.3 and reference documents — instructions for the registration and surveillance of congenital anomalies (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf).
14. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J 2009;51:171-84.
15. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. Pharmacoepidemiol Drug Saf 2012;21:Suppl 2:69-80.
16. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 1. Teratology. Obstet Gynecol 2009;113:166-88. [Erratum, Obstet Gynecol 2009;113: 1377.]
17. Chan RL, Olshan AF, Savitz DA, et al. Severity and duration of nausea and vomiting symptoms in pregnancy and spontaneous abortion. Hum Reprod 2010;25: 2907-12.
18. Weigel RM, Weigel MM. Nausea and vomiting of early pregnancy and pregnancy outcome: a meta-analytical review. Br J Obstet Gynaecol 1989;96:1312-8.
19. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol 2002;186:Suppl:S256-S261.
20. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15:291-303.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/faq_clinical.html.