ORIGINAL ARTICLE

Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects

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ABSTRACT

BACKGROUND

Symptoms of gastroesophageal reflux are common in pregnancy, but there are limited data on the risk of birth defects associated with exposure to proton-pump inhibitors (PPIs) in early pregnancy.

METHODS

We conducted a cohort study to assess the association between exposure to PPIs during pregnancy and the risk of major birth defects among all infants born alive in Denmark between January 1996 and September 2008. We linked data from nationwide registries, including individual-level information on exposure to PPIs (prescriptions), birth defects, and potential confounders. Major birth defects, diagnosed within the first year of life, were categorized according to the standardized classification scheme of the European surveillance of congenital anomalies (EUROCAT). Our primary analyses assessed the use of PPIs from 4 weeks before conception through 12 weeks of gestation and from 0 through 12 weeks of gestation (first trimester).

RESULTS

Among 840,968 live births, 5082 involved exposure to PPIs between 4 weeks before conception and the end of the first trimester of pregnancy. There were 174 major birth defects in infants whose mothers had been exposed to PPIs during this period (3.4%), as compared with 21,811 in the group whose mothers had not been exposed (2.6%) (adjusted prevalence odds ratio, 1.23; 95% confidence interval [CI], 1.05 to 1.44). In analyses limited to exposure during the first trimester, there were 118 major birth defects among 3651 infants exposed to PPIs (3.2%), and the adjusted prevalence odds ratio was 1.10 (95% CI, 0.91 to 1.34). The risk of birth defects was not significantly increased in secondary analyses of exposure to individual PPIs during the first trimester or in analyses limited to the offspring of women who had filled PPI prescriptions and received enough doses to have a theoretical chance of first-trimester exposure.

CONCLUSIONS

In this large cohort, exposure to PPIs during the first trimester of pregnancy was not associated with a significantly increased risk of major birth defects. (Funded by the Danish Medical Research Council and the Lundbeck Foundation.)

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N Engl J Med 2010;363:2114-23.

Symptoms of gastroesophageal reflux are common in pregnant women as early as the first trimester of pregnancy.[1,2] Proton-pump inhibitors (PPIs) are the most efficacious drugs for the treatment of gastroesophageal reflux[3] and are therefore prescribed for pregnant women who have this condition. Furthermore, given the prevalent use of PPIs in the community, the fact that PPIs are now sold as over-the-counter drugs, and the fact that many pregnancies are unplanned, a large number of women may be exposed to these drugs in the first trimester of pregnancy. Data on the safety of PPI use in pregnancy are, however, rather limited. Although safety studies of PPIs in animals have not shown that there are teratogenic effects, the Food and Drug Administration has classified omeprazole as a category C drug in pregnancy (indicating that studies in animals have shown a risk to the fetus but that adequate data in humans are not available) because of toxic effects on animal embryos and fetuses when the drug is given at high doses.[4,5] All other PPIs are classified as category B drugs (indicating that studies in animals have not shown a risk to the fetus but that adequate data in humans are not available).[1] A recent meta-analysis of seven studies involving a total of 1530 women exposed to PPIs in the first trimester showed that there was no significant increase in the risk of birth defects.[6] The vast majority of exposures to PPIs were to omeprazole. Clinical data on the safety of exposure to other PPIs during pregnancy are very limited.[7-11] We conducted a nationwide, registry-based cohort study to assess associations between the use of PPIs in early pregnancy and major birth defects.

Methods

Sources of Data

We used data from the Medical Birth Register,[12] the Prescription Drug Register,[13] the National Patient Register,[14] the Central Person Register,[15] and Statistics Denmark (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Individual-level data were linked among registries with the use of the personal identification number assigned to all inhabitants in Denmark. The study was approved by the Danish Data Protection Agency. Because this was a registry study, approval from an ethics committee and informed consent were not required.

Using the Medical Birth Register, we identified a cohort of all live-born infants in Denmark from January 1, 1996, through September 30, 2008. We calculated the date of conception by subtracting the gestational age from the date of birth. When information on the gestational age was missing (for 0.9% of the births), we imputed the median age for the cohort, 280 days. The Medical Birth Register estimates the gestational age on the basis of the mother's last menstrual period, corrected with the use of ultrasonographic measurements. (Most pregnant women in Denmark undergo ultrasonography.[16]) A validation study of gestational-age registration in the Medical Birth Register showed that 87% of the recorded ages were consistent with those obtained from medical records if consistency was defined as within 1 week.[17] In cases in which there was a discrepancy, the registry tended to overestimate the gestational age, but rarely by more than 1 week.

The Prescription Drug Register provided information on all PPI prescriptions filled by women in the cohort between 4 weeks before conception and delivery. PPIs were prescription-only drugs during the majority of the period covered by the study. Omeprazole and lansoprazole became available as over-the-counter drugs on December 4, 2006, and May 21, 2007, respectively.

Cases of birth defects were identified with the use of the National Patient Register. A review of the medical records of a random sample of 110 infants identified in the National Patient Register as having birth defects estimated that the overall predictive value for registered diagnoses of birth defects (calculated as the number of infants in the registry with a validated diagnosis of a birth defect divided by the total number of infants recorded in the registry as having a birth defect) was 88%.[18] In another investigation, involving 418 infants, the predictive value for registered diagnoses of cardiac malformations was 89%.[19] We accessed data from the National Patient Register for the period from January 1996 through March 2009. In the case of multiple births, each child was considered in the analyses. Major birth defects were defined according to the EUROCAT (European surveillance of congenital anomalies) classification for subgroups of major congenital anomalies,[20] with some modifications, such as the exclusion of genetic syndromes and chromosomal aberrations (for details, see the Supplementary Appendix). Minor

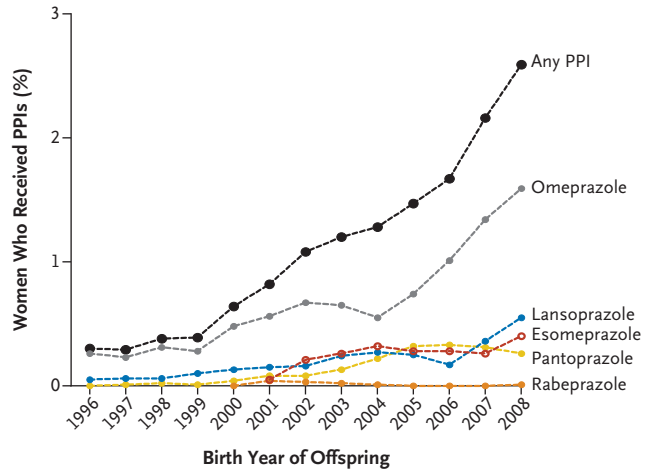

Figure 1. Percentage of Women Receiving Prescriptions for Proton-Pump Inhibitors (PPIs) during Pregnancy, According to the Birth Year of Their Offspring.

anomalies were excluded in accordance with guidelines from EUROCAT.[21]

We obtained information on the following potential confounders: birth year; history of birth defects in siblings; mother's age at conception, parity, smoking status, place of birth, place of residence, educational level, and socioeconomic class; mother's hospitalization for an infectious disease in the first trimester, genitourinary tract infections in the first trimester, diabetes mellitus, epilepsy, or gastric or duodenal ulcer; and mother's use during the first trimester of antiepileptic drugs, benzodiazepines, beta-blockers, oral contraceptives, analgesic agents, angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers, selective serotonin-reuptake inhibitors, glucocorticoids, isotretinoin, and statins (for details, see the Supplementary Appendix). In a subcohort of 96,793 women who were part of the Danish National Birth Cohort study,[22] we accessed self-reported data on body-mass index and

Table 1. Characteristics of the Study Participants.*

Characteristic	Exposed to PPIs (N=5082)†		Not Exposed to PPIs (N=832,031)‡
	Weeks 1–4 before Conception (N=1969)	First Trimester (N=3651)	
	number (percent)		
Birth year			
1996–1998	173 (8.8)	328 (9.0)	201,141 (24.2)
1999–2001	329 (16.7)	520 (14.2)	197,904 (23.8)
2002–2004	530 (26.9)	961 (26.3)	191,647 (23.0)
2005–Sept. 2008	937 (47.6)	1842 (50.5)	241,339 (29.0)
Maternal age at conception			
<18 yr	6 (0.3)	7 (0.2)	2,305 (0.3)
18–24 yr	231 (11.7)	469 (12.8)	112,099 (13.5)
25–29 yr	592 (30.1)	1092 (29.9)	290,329 (34.9)
30–34 yr	675 (34.3)	1240 (34.0)	293,722 (35.3)
35–39 yr	378 (19.2)	668 (18.3)	115,273 (13.9)
40–44 yr	80 (4.1)	160 (4.4)	17,706 (2.1)
≥45 yr	7 (0.4)	15 (0.4)	597 (0.1)
Parity			
0	806 (40.9)	1436 (39.3)	351,889 (42.3)
1	587 (29.8)	1116 (30.6)	299,337 (36.0)
2	314 (15.9)	604 (16.5)	114,545 (13.8)
≥3	214 (10.9)	421 (11.5)	42,502 (5.1)

Table 1. (Continued.)

Characteristic	Exposed to PPIs (N=5082)†		Not Exposed to PPIs (N=832,031)‡
	Weeks 1–4 before Conception (N=1969)	First Trimester (N=3651)	
	number (percent)		
Years of maternal education			
9	577 (29.3)	1079 (29.6)	176,026 (21.2)
12	228 (11.6)	417 (11.4)	107,230 (12.9)
>12	1077 (54.7)	1938 (53.1)	512,984 (61.7)
Maternal employment	1235 (62.7)	2239 (61.3)	620,091 (74.5)
Smoking during pregnancy	458 (23.3)	764 (20.9)	159,987 (19.2)
History of any birth defects in siblings	152 (7.7)	267 (7.3)	39,320 (4.7)
Maternal medical conditions			
Diabetes	62 (3.1)	91 (2.5)	9,017 (1.1)
Epilepsy	19 (1.0)	40 (1.1)	4,603 (0.6)
Gastric or duodenal ulcer	70 (3.6)	92 (2.5)	1,398 (0.2)
Prescription drug use during first trimester			
Antiepileptic agent	14 (0.7)	39 (1.1)	2,732 (0.3)
Benzodiazepine	35 (1.8)	73 (2.0)	3,142 (0.4)
Selective serotonin-reuptake inhibitor	70 (3.6)	173 (4.7)	7,240 (0.9)
Statin	5 (0.3)	7 (0.2)	105 (<0.1)
ACE inhibitor or ARB	3 (0.2)	9 (0.2)	406 (<0.1)
Beta-blocker	29 (1.5)	37 (1.0)	2,680 (0.3)
Analgesic agent	139 (7.1)	237 (6.5)	8,478 (1.0)
Glucocorticoid, including topical and inhaled	228 (11.6)	424 (11.6)	51,372 (6.2)

* The study cohort included mothers and 840,968 live-born infants throughout Denmark from January 1996 through September 2008. Data on parity are missing for 2 to 3% of the mothers, data on maternal education for 4%, data on employment for 0.2 to 0.7%, and data on smoking during pregnancy for 4%. Because of rounding, percentages may not total 100. Table 2 in the Supplementary Appendix provides more detailed characteristics of the study participants, including those of women who were exposed to PPIs in the second and third trimesters of pregnancy (4770 women). ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† The group of women who were exposed to PPIs includes all women who were exposed at any time during the period from 4 weeks before conception through the end of the first trimester. Some women were exposed to proton-pump inhibitors (PPIs) in more than one time window.

‡ The group of women who were not exposed to PPIs includes all women who were not exposed at any time during their pregnancy.

alcohol consumption. We did not have data on maternal use of folic acid supplements.

STATISTICAL ANALYSIS

We used logistic regression, performed with the PROC GENMOD procedure in SAS software (version 9.1), to estimate the prevalence odds ratios, with 95% confidence intervals, for major birth defects in infants born to women who were exposed to PPIs as compared with those in infants born to women who were not exposed to PPIs. We calculated propensity scores on the basis of potential confounders that were significant risk factors ($P<0.05$) for major birth defects in univariate analyses (with missing values excluded for estimates of P values) (Table 1 in the Supplementary Appendix). The main results were adjusted for propensity scores categorized in quintiles. When constructing the propensity scores, we used mode imputation for variables with

Table 2. Association between the Use of Proton-Pump Inhibitors during Pregnancy and Major Birth Defects.*

PPI Exposure	Exposure during Weeks 1–4 before Conception				Exposure during First Trimester	
	Live Births	Birth Defects	Unadjusted Prevalence Odds Ratio (95% CI)	Adjusted Prevalence Odds Ratio (95% CI)†	Live Births	Birth Defects
	no.	*no. (%)*			*no.*	*no. (%)*
Not exposed to any PPI	838,999	21,908 (2.6)	Reference	Reference	837,317	21,867 (2.6)
Exposed to any PPI‡	1969	77 (3.9)	1.52 (1.21–1.91)	1.39 (1.10–1.76)	3,651	118 (3.2)
Omeprazole	592	17 (2.9)	1.10 (0.68–1.78)	1.06 (0.65–1.73)	1,800	52 (2.9)
Pantoprazole	392	13 (3.3)	1.28 (0.74–2.22)	1.09 (0.62–1.92)	549	21 (3.8)
Lansoprazole	541	29 (5.4)	2.11 (1.45–3.07)	1.91 (1.30–2.80)	794	28 (3.5)
Rabeprazole	32	2 (6.2)	2.48 (0.59–10.39)	1.97 (0.44–8.72)	42	3 (7.1)
Esomeprazole	439	17 (3.9)	1.50 (0.92–2.44)	1.35 (0.82–2.23)	668	23 (3.4)

* The study cohort included mothers and 840,968 live-born infants throughout Denmark from January 1996 through September 2008. Use of proton-pump inhibitors (PPIs) was defined as the filling of a PPI prescription at any time in a distinct exposure-time window, and the timing of exposure was defined according to the first day of use.

† The adjusted prevalence odds ratio was adjusted for propensity score and the effects of exposure to PPIs in either of the other two exposure-time windows.

‡ Some women were exposed to more than one PPI; therefore, the sum of the number of women exposed to individual PPIs is larger than the total number of exposed women.

missing values. For the primary outcome measure — all major birth defects — we combined all subgroups of defects. Children were followed for a maximum of 1 year after birth. Any filling of a PPI prescription was considered to indicate exposure. To increase the sensitivity for inclusion of women who had started taking PPIs shortly before conception, the timing of exposure was first set as any exposure between 4 weeks before conception and the end of the first trimester (12 weeks). The cohort of women with exposure in early pregnancy was then divided into women who had filled PPI prescriptions in the 4-week period before conception and those who had filled prescriptions during the first trimester. An analysis of exposure during the second and third trimesters was performed for comparison. The timing of exposure was defined according to the date the prescription was filled, and a pregnancy could contribute to more than one exposure-time window. In cases in which a mother was exposed in more than one exposure-time window, corresponding prevalence odds ratios (except for crude estimates) were adjusted for the effects of each exposure on the other.

In secondary analyses, we evaluated subgroups of birth defects according to organ system. In the three exposure-time windows, our prespecified subgroup analyses included 5 PPIs and 13 birth-defect subgroups. Since no correction for multiple testing was applied, 2 to 3 of the 54 tests would be expected to be significant by chance alone. In post hoc analyses, we assessed associations between exposure to any PPI or to omeprazole and the 10 most common specific defects, selected according to EUROCAT statistics for major defects among live-born infants in Europe from 1980 to 2008 (prevalence tables at www.eurocat-network.eu) in the three time windows. Three of these 60 tests would be expected to be significant by chance alone.

RESULTS

STUDY COHORT

The study cohort comprised 840,968 live births (including 34,925 multiple births). Overall, 21,985 cases of major birth defects were diagnosed during the first year of life (2.6%). The prevalence of the use of PPIs during pregnancy increased over time; omeprazole was the most commonly prescribed PPI (Fig. 1). Key characteristics of the cohort members according to PPI-exposure status are presented in Table 1 (with additional details provided in Table 2 in the Supplementary Appendix).

Exposure during First Trimester		Exposure during Second and Third Trimesters			
Unadjusted Prevalence Odds Ratio (95% CI)	Adjusted Prevalence Odds Ratio (95% CI)†	Live Births	Birth Defects	Unadjusted Prevalence Odds Ratio (95% CI)	Adjusted Prevalence Odds Ratio (95% CI)†
		no.	*no. (%)*		
Reference	Reference	836,198	21,836 (2.6)	Reference	Reference
1.25 (1.0–1.50)	1.10 (0.91–1.34)	4,770	149 (3.1)	1.20 (1.02–1.42)	1.09 (0.92–1.29)
1.11 (0.84–1.46)	1.05 (0.79–1.40)	3,755	108 (2.9)	1.10 (0.91–1.34)	1.04 (0.85–1.26)
1.48 (0.96–2.29)	1.33 (0.85–2.08)	325	13 (4.0)	1.55 (0.89–2.70)	1.39 (0.79–2.44)
1.36 (0.93–1.99)	1.13 (0.77–1.67)	415	19 (4.6)	1.79 (1.13–2.83)	1.55 (0.97–2.47)
2.87 (0.89–9.27)	2.14 (0.60–7.68)	9	1 (11.1)	4.66 (0.58–37.23)	3.27 (0.37–29.12)
1.33 (0.88–2.01)	1.19 (0.77–1.84)	391	11 (2.8)	1.08 (0.59–1.96)	0.92 (0.50–1.70)

PREVALENCE OF BIRTH DEFECTS

A total of 174 of 5082 infants (3.4%) whose mothers were exposed to PPIs at any time between 4 weeks before conception and the end of the first trimester (defined as 12 weeks after conception) had a diagnosis of a major birth defect, as compared with 21,811 of 835,886 infants (2.6%) in the unexposed group (unadjusted prevalence odds ratio, 1.31, 95% confidence interval [CI], 1.12 to 1.53; prevalence odds ratio adjusted for propensity score, 1.23, 95% CI, 1.05 to 1.44). Prevalence odds ratios for the association between the use of any PPI or the use of specific PPIs and the occurrence of major birth defects in different exposure-time windows are shown in Table 2. A total of 118 of 3651 infants (3.2%) who were exposed to PPIs at any time during the first trimester, which was the main exposure-time window of interest, had a diagnosis of a major birth defect, as compared with 21,867 of 837,317 infants (2.6%) in the unexposed group. There was no significant association between the use of PPIs in the first trimester and the risk of major birth defects (adjusted prevalence odds ratio, 1.10; 95% CI, 0.91 to 1.34). Women who were exposed to PPIs within 4 weeks before conception were at significantly increased risk for having offspring with major birth defects (adjusted prevalence odds ratio, 1.39; 95% CI, 1.10 to 1.76).

ANALYSES OF INDIVIDUAL PPIS

In subsequent analyses performed for individual PPIs (Table 2), we found no significant associations between the use of any of the specific PPIs during the first trimester and the risk of major birth defects. Lansoprazole was the only PPI for which use within 4 weeks before conception was significantly associated with an increased risk. However, the number of women who were exposed to rabeprazole was very small.

SUBGROUP ANALYSES

In secondary analyses of subgroups of major birth defects according to organ system (Fig. 2), there was no significant increase in the prevalence of birth defects in the offspring of women exposed to PPIs in the first trimester, although exposure within 4 weeks before conception was associated with an elevated risk of heart and urinary tract defects. Post hoc analyses restricted to omeprazole showed no significant associations with any subgroup of birth defects in any exposure-time window (see the figure in the Supplementary Appendix). Post hoc analyses of the 10 most common specific major defects showed no significant association between exposure during the first trimester to any PPI or to omeprazole specifically and any of the 10 defects (Table 3 in the Supplementary Appendix). However, these analyses were based on a small number of cases.

ADDITIONAL ANALYSES

We performed several additional analyses to test the robustness of our results. We conducted prespecified analyses of data from women exposed within 4 weeks before conception, taking into account the number of daily defined doses in the prescription (assuming that the mother took the

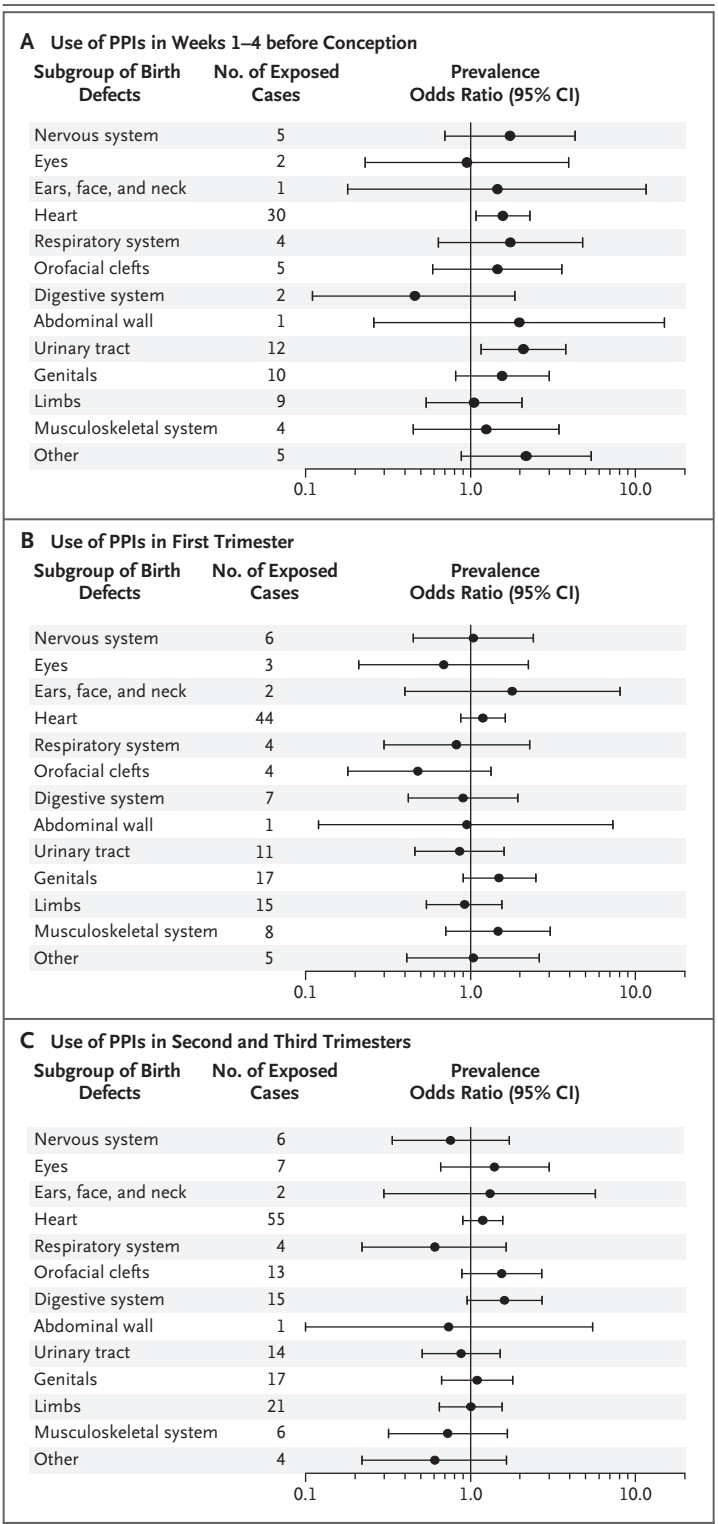

Figure 2. Associations between the Use of Proton-Pump Inhibitors (PPIs) during Pregnancy and Subgroups of Major Birth Defects.

The scale of the prevalence odds ratio is a log scale.

drug daily and took all the doses contained in the package). Women who had filled prescriptions for PPIs within 4 weeks before conception but had not received enough doses to have a theoretical chance of continued exposure beyond conception were at increased risk for having offspring with major birth defects (adjusted prevalence odds ratio, 1.53; 95% CI, 1.22 to 1.92). Among women who had filled PPI prescriptions and received enough doses to have a theoretical chance of exposure in the first trimester, exposure was not significantly associated with major birth defects (adjusted prevalence odds ratio, 1.12; 95% CI, 0.94 to 1.35).

In post hoc analyses in which alternative exposure-time windows were considered (Table 3), exposure in the period of maximal susceptibility to teratogenic agents — 3 to 8 weeks after conception — was not significantly associated with major birth defects. We also found no significant associations between the use of PPIs during the first trimester and the risk of birth defects in the following additional post hoc analyses: analyses that were restricted to the period when all PPIs were available only by prescription, analyses that included body-mass index and alcohol consumption as covariates in the subgroup of women for whom these data were available, analyses that were restricted to women who refilled PPI prescriptions during the first trimester, and analyses that were restricted to women who used PPIs in the first trimester only (Table 3) (see the Supplementary Appendix for details of these and other post hoc analyses). Furthermore, risk estimates for birth defects associated with exposure to PPIs at any time within 12 weeks before conception were not materially different from those for exposure within 4 weeks before conception (Supplementary Appendix).

DISCUSSION

This nationwide cohort study showed that there were no significant associations between the use of PPIs during the first trimester and the risk of major birth defects. In subgroup analyses, estimates of risk were similar across the individual PPIs, with the exception of rabeprazole, for which there were limited data. In secondary analyses, we found no significant associations between the use of PPIs during the first trimester and subgroups of major birth defects according to organ system.

Table 3. Alternative Analyses of the Association between Exposure to Proton-Pump Inhibitors in Pregnancy and the Risk of Major Birth Defects.*

Analysis	Adjusted Prevalence Odds Ratio (95% CI)
Alternative exposure-time windows†	
2–4 wk before conception	1.51 (1.11–2.05)
2 wk before to 2 wk after conception	1.21 (0.95–1.56)
3–8 wk after conception	1.04 (0.81–1.33)
9 wk after conception to birth	1.09 (0.93–1.28)
Restricted to study period when all PPIs were prescription only†	1.02 (0.81–1.29)
Restricted to women who refilled prescriptions in first trimester†	1.15 (0.74–1.80)
Restricted to women who used PPIs in the first trimester only†	1.16 (0.81–1.66)
Adjusted for body-mass index and alcohol use‡	1.15 (0.49–2.70)

* These were post hoc analyses. If not stated otherwise, the prevalence odds ratios refer to exposure to proton-pump inhibitors (PPIs) during the first trimester. Additional alternative analyses and details are provided in the Supplementary Appendix.

† This analysis was adjusted for the propensity score.

‡ This analysis was performed on data from a subcohort of 96,793 women for whom self-reported information on body-mass index and alcohol use was available. The unadjusted prevalence odds ratio for this analysis was 1.16 (95% CI, 0.49 to 2.73).

Our initial analysis defined exposure to PPIs as the filling of a prescription at some time between 4 weeks before conception and the end of the first trimester, since we wanted to include data from women who had started taking PPIs before conception and continued taking them during early pregnancy. When exposure within 4 weeks before conception was included in the main analysis, there was a significant association between exposure to PPIs and major birth defects. When separate analyses were performed on data from women who filled prescriptions within 4 weeks before conception and from those who filled prescriptions in the first trimester, only women who received PPIs within 4 weeks before conception were at increased risk for having infants with birth defects. Furthermore, when the analyses accounted for the daily doses of PPIs in prescriptions filled before conception, only infants whose mothers took PPIs before the estimated date of conception but did not receive enough doses to have a theoretical chance of continued exposure beyond conception were at increased risk for birth defects. Analyses of data from alternative exposure-time windows supported the main results. Although some misclassification of the timing of exposure is possible[17] given the uncertainty regarding the dates of conception, the results of analyses focusing on exposures during weeks 3 to 8 after presumed conception were consistent with the main results involving exposure during the 12 weeks after presumed conception.

The observed association between exposure to PPIs within the month before conception and major birth defects may represent unmeasured confounding or may have been due to chance. The plasma half-lives of PPIs range between 1 and 2 hours; therefore, it is unlikely that there was a carryover effect from exposure before conception into early pregnancy.

Our results with respect to the effect of exposure to PPIs during the first trimester are consistent with findings from previous research involving various types of cohorts, including registry-based historical cohorts, prospective cohorts of mothers seeking advice from teratology services, and cohorts identified from pregnancy registries.[7-9,11,23,24] A meta-analysis of these studies, which was based on 1530 women exposed to PPIs in early pregnancy, showed that there was no significant increase in the risk of birth defects associated with exposure to PPIs (odds ratio, 1.12; 95% CI, 0.86 to 1.45).[6] Our study, which had a substantially larger cohort than the samples in all the previous reports collectively, confirms the findings from previous reports regarding omeprazole and extends those findings to other PPIs.

Our study covered a period of 13 years and

involved a nationwide population and independent ascertainment of exposure and outcome. Several previous studies[7,8,23] did not follow children beyond the immediate neonatal period, and defects diagnosed later would not have been included in the analyses, whereas our study had a 1-year follow-up period for birth defects. Although we adjusted for several potential confounders, it is possible that there were confounding factors that we did not identify. Our primary concern would be factors that could have masked a risk of birth defects associated with the use of PPIs. Given the size of the cohort, such factors would have had to be common or would have had to be strongly associated with both the use of PPIs and a reduced risk of defects. We consider it unlikely that there were unmeasured confounding factors that met these criteria.

We used a registry-based case-finding strategy for the identification of birth defects, and the outcome may have been subject to minor misclassification.[18] Although any misclassification was probably random, it could bias the results toward no effect. We used filled prescriptions as proxies for exposure to PPIs. If women did not take the dispensed PPIs, however, the results would be biased toward no effect, and teratogenic effects, if present, could be obscured. Omeprazole and lansoprazole became available as over-the-counter drugs during the last years of the study. Misclassification of exposure on the basis of the use of over-the-counter preparations by women who were classified as not having been exposed to PPIs could similarly bias the results toward no effect. However, the analysis that was restricted to the period when PPIs were available by prescription only provides further reassurance that misclassification of exposure was not an important source of bias.

The main outcome measure — all major birth defects combined — may have some shortcomings. Teratogens typically cause specific defects or groups of defects and do not necessarily increase the rate of birth defects overall.[25] Nevertheless, composite outcomes are often used in studies of birth defects[26,27] and offer opportunities to identify previously unknown or unsuspected associations. A limitation of cohort studies of births defects is that specific defects are uncommon, and therefore the power to detect associations with individual defects is limited.[25] Our analyses of subgroups of birth defects should therefore be interpreted with caution. Large case–control studies[28,29] may provide opportunities to investigate specific defects with sufficient power.

Most studies of the safety of PPIs during pregnancy have involved women exposed to omeprazole. The results of our study add to the data supporting the safety of this drug with regard to birth defects. Moreover, research that showed no increase in the risk of spontaneous abortions or preterm births associated with the use of PPIs was also based largely on exposure to omeprazole.[6] Further study is needed to address the safety of PPIs with regard to perinatal outcomes, as well as the outcomes when PPIs are taken during lactation, and to address specific birth defects and potential long-term risks associated with individual PPIs.[30]

In conclusion, in this nationwide cohort study, we found no significant association between the use of PPIs during the first trimester of pregnancy and the risk of major birth defects. These results provide reassurance that PPIs, and omeprazole in particular, can be used relatively safely during the first trimester.

Supported by the Danish Medical Research Council and the Lundbeck Foundation.

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

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