ORIGINAL ARTICLE

Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D., Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D., Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A., Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

ABSTRACT

BACKGROUND

Whether the use of selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants during pregnancy is associated with an increased risk of congenital cardiac defects is uncertain. In particular, there are concerns about a possible association between paroxetine use and right ventricular outflow tract obstruction and between sertraline use and ventricular septal defects.

METHODS

We performed a cohort study nested in the nationwide Medicaid Analytic eXtract for the period 2000 through 2007. The study included 949,504 pregnant women who were enrolled in Medicaid during the period from 3 months before the last menstrual period through 1 month after delivery and their liveborn infants. We compared the risk of major cardiac defects among infants born to women who took antidepressants during the first trimester with the risk among infants born to women who did not use antidepressants, with an unadjusted analysis and analyses that restricted the cohort to women with depression and that used propensity-score adjustment to control for depression severity and other potential confounders.

RESULTS

A total of 64,389 women (6.8%) used antidepressants during the first trimester. Overall, 6403 infants who were not exposed to antidepressants were born with a cardiac defect (72.3 infants with a cardiac defect per 10,000 infants), as compared with 580 infants with exposure (90.1 per 10,000 infants). Associations between antidepressant use and cardiac defects were attenuated with increasing levels of adjustment for confounding. The relative risks of any cardiac defect with the use of SSRIs were 1.25 (95% confidence interval [CI], 1.13 to 1.38) in the unadjusted analysis, 1.12 (95% CI, 1.00 to 1.26) in the analysis restricted to women with depression, and 1.06 (95% CI, 0.93 to 1.22) in the fully adjusted analysis restricted to women with depression. We found no significant association between the use of paroxetine and right ventricular outflow tract obstruction (relative risk, 1.07; 95% CI, 0.59 to 1.93) or between the use of sertraline and ventricular septal defects (relative risk, 1.04; 95% CI, 0.76 to 1.41).

CONCLUSIONS

The results of this large, population-based cohort study suggested no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester. (Funded by the Agency for Healthcare Research and Quality and the National Institutes of Health.)

From the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (K.F.H., J.A., J.M.F., H.M., R.L., M.K., S.S.), the Department of Epidemiology, Harvard School of Public Health (K.P., S.H.-D.), the Center for Women's Mental Health, Massachusetts General Hospital (L.S.C.), and the Medical Genetics Unit, MassGeneral Hospital for Children (L.B.H.) — all in Boston; and Duke University School of Medicine, Durham, NC (S.S.). Address reprint requests to Dr. Huybrechts at the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont St., Suite 3030, Boston, MA 02120, or at khuybrechts@partners.org.

N Engl J Med 2014;370:2397-407.
DOI: 10.1056/NEJMoa1312828

Clinical depression occurs in 10 to 15% of pregnant women.[1] The use of antidepressant medications during pregnancy has increased steadily over time, with reported prevalences of 8 to 13% in the United States.[2-4] Selective serotonin-reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy.[4] In 2005, on the basis of early results of two epidemiologic studies, the Food and Drug Administration (FDA) warned health care professionals that early prenatal exposure to paroxetine may increase the risk of congenital cardiac malformations, and the FDA reclassified the drug to pregnancy category D (evidence of human fetal risk, but benefits may warrant use).[5] Most malformations cited in the early reports leading to the FDA warning were septal defects. Since then, several studies have evaluated the teratogenicity of SSRIs and other antidepressants,[6-19] but considerable controversy remains regarding whether this is a "serious concern or much ado about little," as noted in an editorial published with two of the reports.[13,14,20]

Studies have shown diverse associations, often in the context of multiple comparisons. Yet, at least two studies have shown a doubled or tripled risk of right ventricular outflow tract obstruction associated with paroxetine use[13,14] and of ventricular septal defects associated with sertraline use.[13,19] A meta-analysis estimated a 50% increase in the prevalence of cardiac defects overall with paroxetine use during the first trimester.[21] It has remained unclear, however, whether these associations are causal or due to systematic error or chance. We conducted a cohort study using a large national database of publicly insured pregnant women and adolescents in the United States to assess the risk of congenital cardiac defects after the use of specific antidepressants, with attention to the potential for confounding by the underlying depression and associated factors.

Methods

Data Source and Study Cohort

The study cohort was drawn from the Medicaid Analytic eXtract for 46 U.S. states and Washington, D.C., for the period of 2000 through 2007. Montana and Connecticut were excluded because of difficulty in linking data for mothers and infants, Michigan was excluded because of incomplete data, and data from Arizona were not available. The Medicaid Analytic eXtract data set contains individual-level demographic and Medicaid enrollment information, as well as data on all physician services and hospitalizations and the accompanying diagnoses and procedures and all filled outpatient medication prescriptions.

The development of our study cohort has been described previously.[22] Briefly, we identified all completed pregnancies in women and adolescents 12 to 55 years of age (hereafter, "women") and linked these pregnancies to liveborn infants. Using a validated algorithm,[23] we estimated the date of the last menstrual period on the basis of the delivery date and diagnostic codes indicative of preterm delivery. Finally, we required all the women to be eligible for Medicaid, without supplementary private insurance or restricted benefits, from 3 months before the last menstrual period through 1 month after delivery. We excluded pregnancies in which the infant had received a diagnosis of a chromosomal abnormality (1609 pregnancies) and pregnancies in which the mother had been treated with known teratogens during the first trimester (i.e., lithium, antineoplastic agents, retinoids, and thalidomide; 2476 pregnancies).

Study Conduct

The study was approved by the institutional review board of Brigham and Women's Hospital, and the need for informed consent was waived. The authors vouch for the accuracy and completeness of the analyses reported as well as for the fidelity of the report to the study protocol.

Antidepressant Medications

The etiologically relevant window for exposure extended from the date of the last menstrual period through day 90 of pregnancy (first trimester). We determined maternal use of antidepressants by a review of pharmacy dispensing records, using the dispensing date and the number of days of supply. Women were considered to have had exposure if the days of supply overlapped with the first trimester. We defined the following exposure categories: any SSRI, paroxetine, sertraline, fluoxetine, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), bupropion, and other antidepressants (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The reference group consisted of women without exposure to antidepressants during the first trimester.

CARDIAC MALFORMATIONS

Congenital cardiac malformations were identified on the basis of the presence of inpatient or outpatient diagnostic codes from the *International Classification of Diseases, Ninth Revision* (ICD-9), in the maternal or infant records during the first 90 days after delivery. We used both maternal and infant codes because an infant's claims may be recorded under the mother's identification number for the first several months after birth.[24] On the basis of previously reported associations,[13,14,19] outcomes were grouped in the following categories: any cardiac malformation, right ventricular outflow tract obstruction, ventricular septal defect, and other cardiac malformation (Table S2 in the Supplementary Appendix). We excluded anomalies related to prematurity (e.g., patent ductus arteriosus, pulmonary-valve stenosis, and anomalies of the pulmonary artery in preterm infants).[25] A given outcome was considered to be present if there was more than one date with the respective diagnostic codes recorded or if there was one diagnostic code and a code for a cardiac procedure or surgery (Table S3 in the Supplementary Appendix). The positive predictive values for these outcome definitions did not differ substantially according to exposure and ranged from 66.7 to 79.5% in a conservative validation study that was based on review of primary medical records in a subset of cases.[26]

COVARIATES

The information on covariates that were being taken into consideration in the adjustment for confounding or that were being used for stratification was obtained during the baseline period (from the time before the last menstrual period through the end of the first trimester). In addition to sociodemographic information (year of delivery, state of residence, age, race, and parity), we considered known or suspected risk factors for congenital cardiac malformations and proxies for such risk factors: multiple gestation, chronic maternal illness (hypertension, diabetes, epilepsy, and renal disease), use of suspected teratogenic medications, use of other psychotropic medications (anticonvulsant, antipsychotic, anxiolytic, and hypnotic agents; other benzodiazepines; and barbiturates), use of antidiabetic and antihypertensive medications, and the number of distinct prescription drugs used, excluding antidepressants, as a general marker of coexisting conditions.[27] To address confounding by the underlying indication, we considered proxies for depression severity (number of depression diagnoses received as an outpatient and as an inpatient) and other indications for antidepressant use (other mental health disorders, pain-related diagnoses, sleep disorders, the premenstrual tension syndrome, smoking, and the chronic fatigue syndrome).

STATISTICAL ANALYSIS

We compared the distributions of sociodemographic, clinical, and health care utilization characteristics among the various exposure groups, and we calculated the absolute risks of cardiac malformations. Logistic-regression analysis was used to estimate odds ratios for cardiac malformations and their corresponding 95% confidence intervals. Because the odds ratio is an excellent approximation of the risk ratio in the case of rare outcomes, the results are referred to as relative risks.[28] Use of the robust variance estimator to account for correlations within women with multiple pregnancies did not change the confidence intervals appreciably, so correlation structures were omitted from all the analyses.

Results are presented for analyses performed according to three levels of adjustment: an unadjusted analysis; an analysis restricted to women with a depression diagnosis, to control for the potential effect of the underlying illness or factors associated with it; and an analysis restricted to women with a depression diagnosis and performed with the use of propensity-score stratification to further control for proxies of depression severity and other potential confounders.[29] Propensity scores were derived from the predicted probability of treatment estimated in a logistic-regression model that contained all the covariates listed above without additional variable selection. We created 100 equally sized propensity-score strata, dropped uninformative strata (i.e., all strata that did not contain at least one treated woman and one untreated woman), and stratified the outcome models according to these propensity-score strata. In all cases, less than 0.5% of treated women and less than 0.1% of untreated women were included in the dropped strata.

In confirmatory analyses, we used a high-dimensional propensity-score algorithm, which evaluates thousands of diagnoses, procedures, and pharmacy-claim codes to identify and prioritize covariates that serve as proxies for unmeasured

confounders. A total of 200 empirically identified confounders were selected and were combined with investigator-identified covariates to improve adjustment for confounding.[30] No adjustments were made for multiple comparisons.

We performed prespecified subgroup and sensitivity analyses to evaluate the robustness of the primary results (for any cardiac malformation). Because the cohort we studied was younger and more racially diverse than cohorts in previous studies,[13,14] we tested for effect modification according to age (<30 years vs. ≥30 years) and race or ethnic group (white vs. nonwhite). We conducted dose–response analyses for low, medium, and high doses of antidepressants using the first and highest doses dispensed (Table S4 in the Supplementary Appendix).[31] In the analysis of SSRIs, we stratified the analysis according to the use of just that drug class versus the use of multiple antidepressant classes.

To evaluate the effect of potential misclassification of exposure, we redefined exposure status as having had one or more prescriptions filled during the first trimester (as compared with days of supply that overlap with the first trimester); we redefined the reference group as women with no antidepressant exposure throughout pregnancy. To evaluate the effect of potential misclassification of outcome, we restricted the outcome to inpatient diagnoses only and extended infant follow-up to 1 year. We corrected odds ratios for outcome misclassification using sensitivities and specificities consistent with the positive predictive values estimated in the internal validation study.[26,32] To further assess whether outcomes were well captured, we evaluated some well-known associations in our data set — in particular, associations between cardiac malformations and maternal diabetes, use of an anticonvulsant agent, or multifetal pregnancy.[33]

RESULTS

CHARACTERISTICS OF THE STUDY COHORT

We identified 949,504 eligible pregnancies. Women could have contributed more than 1 pregnancy to the cohort. During the first trimester, 64,389 women (6.8%) used an antidepressant: 46,144 women (4.9%) were exposed to an SSRI, 5954 (0.6%) to a tricyclic antidepressant, 6904 (0.7%) to an SNRI, 8856 (0.9%) to bupropion, and 7055 (0.7%) to other antidepressants. Among the SSRIs, sertraline was used most frequently (in 14,040 women), followed by paroxetine (in 11,126) and fluoxetine (in 11,048).

As compared with women who took no antidepressant, women who filled a prescription for an antidepressant were older, had greater health care utilization, and were more likely to be white, to use other psychotropic medications, to have a chronic illness (in particular, hypertension or diabetes), and to use suspected teratogenic medications (Table 1). Baseline characteristics were more homogeneous in analyses comparing users of various antidepressant classes than in analyses comparing users of antidepressants with nonusers (Tables S5 through S13 in the Supplementary Appendix).

RISK OF CARDIAC MALFORMATION

Overall, cardiac malformations were diagnosed in 6403 infants who were not exposed to an antidepressant during the first trimester (72.3 cardiac malformations per 10,000 infants), as compared with 580 infants who were exposed (90.1 cardiac malformations per 10,000 infants). This higher unadjusted risk among exposed infants was observed for each of the specific types of malformations considered (Table 2).

In unadjusted analyses, the relative risk of any cardiac malformation was 1.25 with SSRIs (95% confidence interval [CI], 1.13 to 1.38), 0.98 with tricyclic antidepressants (95% CI, 0.72 to 1.32), 1.51 with SNRIs (95% CI, 1.20 to 1.90), 1.19 with bupropion (95% CI, 0.95 to 1.49), and 1.46 with other antidepressants (95% CI, 1.16 to 1.83) (Fig. 1). Increased risks were observed for all three subtypes of cardiac malformation in most exposure groups (Fig. 2).

Restricting the cohort to women with a diagnosis of depression markedly attenuated the associations (Fig. 1 and 2). The C-statistic for the propensity-score models ranged from 0.84 to 0.91, indicating that substantial differences in the characteristics of the patients remained after the cohort was restricted to women with depression. Stratification according to the propensity score ensured that comparisons were made between groups with nearly identical characteristics (Table 1, and Tables S5 through S13 in the Supplementary Appendix).

Adjustment for the propensity score further attenuated the remaining positive associations.

Table 1. Selected Cohort Characteristics of Women with Exposure to an SSRI during the First Trimester and Women without Exposure to an Antidepressant.*

Characteristic	Overall Cohort		Depression-Restricted Cohort†	
	SSRI (N=46,144)	No Exposure (N=885,115)	SSRI (N=36,778)	No Exposure (N=180,564)
Age — yr	25.6±5.9	23.9±5.8	25.5±6.0	25.3±53.1
Race or ethnic group — no. (%)‡				
White	34,098 (73.9)	339,144 (38.3)	27,299 (74.2)	136,506 (75.6)
Black	5,438 (11.8)	313,369 (35.4)	4,193 (11.4)	19,380 (10.7)
Hispanic	4,145 (9.0)	164,317 (18.6)	3,261 (8.9)	15,017 (8.3)
Other or unknown	2,463 (5.3)	68,285 (7.7)	2,025 (5.5)	9,661 (5.4)
Preterm birth — no. (%)§	6,470 (14.0)	98,886 (11.2)	5,250 (14.3)	25,299 (14.0)
Diabetes — no. (%)	1,288 (2.8)	10,628 (1.2)	997 (2.7)	4,957 (2.7)
Use of antidiabetic agent — no. (%)	1,682 (3.6)	15,364 (1.7)	1,303 (3.5)	6,449 (3.6)
Depression — no. (%)	36,783 (79.7)	180,564 (20.4)	36,778 (100.0)	180,564 (100.0)
No. of diagnoses of depression¶				
As an outpatient	2.8±6.5	0.2±2.0	3.5±7.1	3.3±20.3
As an inpatient	0.1±0.3	0.0±0.1	0.1±0.3	0.1±1.0
Use of other psychotropic medication — no. (%)				
Anticonvulsant agent	7,353 (15.9)	31,681 (3.6)	6,654 (18.1)	33,599 (18.6)
Antipsychotic agent	9,534 (20.7)	48,657 (5.5)	8,621 (23.4)	42,987 (23.8)
Anxiolytic agent	3,148 (6.8)	8,189 (0.9)	2,895 (7.9)	14,320 (7.9)
Benzodiazepine	14,560 (31.6)	49,063 (5.5)	12,856 (35.0)	63,100 (34.9)
Other hypnotic agent	13,277 (28.8)	115,608 (13.1)	11,540 (31.4)	56,323 (31.2)
Barbiturate	3,764 (8.2)	26,030 (2.9)	3,097 (8.4)	15,756 (8.7)
Use of suspected teratogen — no. (%)‖	3,508 (7.6)	26,967 (3.0)	2,806 (7.6)	14,345 (7.9)

* Plus–minus values are means ±SD. Data are from the Medicaid Analytic eXtract for the period 2000 through 2007. SSRI denotes selective serotonin-reuptake inhibitor.

† To account for propensity-score strata, the observations of untreated women were weighted according to the distribution of the treated women among the propensity-score strata. One uninformative stratum (containing five women with exposure to an SSRI) was dropped in the propensity-score–stratified analysis.

‡ Race or ethnic group was determined on the basis of information submitted to the Centers for Medicare and Medicaid Services by individual states, which was based on information that had been collected and coded from Medicaid applications.

§ Data on preterm birth were related to the current pregnancy.

¶ The numbers of outpatient and inpatient diagnoses of depression were used as proxies for the severity of depression.

‖ Pregnant women with exposure to known teratogens were excluded from the cohort, although those with exposure to suspected teratogens were included. Suspected teratogens included angiotensin-converting–enzyme inhibitors, fluconazole, aminoglycosides, folic acid antagonists, methimazole, potassium iodide, tetracycline, danazol, misoprostol, statins, warfarin, and propylthiouracil.

The propensity-score–adjusted relative risk of any cardiac malformation was 1.06 among women with exposure to SSRIs (95% CI, 0.93 to 1.22), 0.77 among those with exposure to tricyclic antidepressants (95% CI, 0.52 to 1.14), 1.20 among those with exposure to SNRIs (95% CI, 0.91 to 1.57), 0.92 among those with exposure to bupropion (95% CI, 0.69 to 1.22), and 1.21 among those with exposure to other antidepressants (95% CI, 0.91 to 1.60) (Fig. 1 and 2). We found no significant associations between paroxetine and right ventricular outflow tract obstruction (1.07; 95% CI, 0.59 to 1.93) or between sertraline and ventricular septal defect

Table 2. Absolute Risk of Congenital Cardiac Malformations among Infants Born to Mothers with Antidepressant Exposure and Infants Born to Mothers without Exposure, According to Antidepressant Category in the Overall Cohort.*

Exposure Group	Total No. of Women	Any Cardiac Malformation		Right Ventricular Outflow Tract Obstruction		Ventricular Septal Defect		Other Cardiac Malformation	
		Events	Risk	Events	Risk	Events	Risk	Events	Risk
		no. of affected infants	*no./10,000 infants*	*no. of affected infants*	*no./10,000 infants*	*no. of affected infants*	*no./10,000 infants*	*no. of affected infants*	*no./10,000 infants*
No exposure	885,115	6403	72.3	1045	11.8	3212	36.3	3232	36.5
Any antidepressant	64,389	580	90.1	84	13.0	286	44.4	318	49.4
SSRI	46,144	416	90.2	61	13.2	201	43.6	226	49.0
Paroxetine	11,126	93	83.6	16	14.4	44	39.5	48	43.1
Sertraline	14,040	129	91.9	17	12.1	63	44.9	71	50.6
Fluoxetine	11,048	99	89.6	16	14.5	48	43.4	55	49.8
Tricyclic antidepressant	5,954	42	70.5	8	13.4	24	40.3	18	30.2
SNRI	6,904	75	108.6	12	17.4	39	56.5	38	55.0
Bupropion	8,856	76	85.8	11	12.4	39	44.0	49	55.3
Other antidepressant	7,055	74	104.9	8	11.3	31	43.9	46	65.2

* Data are from the Medicaid Analytic eXtract for the period 2000 through 2007. Infants could have had more than one cardiac malformation. SNRI denotes serotonin–norepinephrine reuptake inhibitor.

(1.04; 95% CI, 0.76 to 1.41). Analyses that used high-dimensional propensity scores yielded essentially the same results (Table S15 in the Supplementary Appendix).

SUBGROUP AND SENSITIVITY ANALYSES

There was no evidence of effect modification according to age or race (Table S16 in the Supplementary Appendix). We did not observe a dose–response relationship either with respect to the first dose or with respect to the highest dose dispensed (Table S17 in the Supplementary Appendix). The relative risk of cardiac malformations associated with the use of SSRIs was similar among users of antidepressant monotherapy (relative risk, 1.04; 95% CI, 0.90 to 1.21) and users of polytherapy (relative risk, 1.17; 95% CI, 0.90 to 1.53). The overall findings were not qualitatively affected when we varied the exposure and outcome definitions (Tables S18 and S19 in the Supplementary Appendix). The shift in effect estimates resulting from correction for predicted outcome misclassification ranged from 1.3 to 9.6% (Table S20 in the Supplementary Appendix). We replicated the well-known associations between cardiac malformations and maternal diabetes (relative risk, 3.7; 95% CI, 3.4 to 4.0), use of an anticonvulsant agent (relative risk, 1.6; 95% CI, 1.3 to 1.8), and multifetal pregnancy (relative risk, 2.9; 95% CI, 2.8 to 3.1).

DISCUSSION

In this cohort of 949,504 pregnant women in the Medicaid program, after adjustment for depression and other potential confounding factors, we found no significant increase in the risk of cardiac malformations among infants born to women who took antidepressants during the first trimester, as compared with infants born to women who did not have exposure to these agents. Furthermore, no significantly increased risks were observed with respect to specific cardiac defects previously hypothesized to be associated with such drug use, specific antidepressant medication classes, or the most commonly used SSRIs.

Our results do not support earlier findings of an association between antidepressant use and cardiac anomalies, in particular findings with respect to the use of paroxetine and sertraline.[13,14,19] In contrast to analyses in earlier studies, our adjusted analyses restricted the cohort to women with a recorded diagnosis of depression in order to mitigate potential confounding by the under-

lying psychiatric illness and associated conditions and behaviors, factors that might increase the risk of structural cardiac malformations by means of several mechanisms. Smoking, alcohol and drug use, poor maternal diet, obesity, and chronic conditions such as diabetes and hypertension are all more common in patients with depression than in those without depression and are potential risk factors for congenital cardiac anomalies.[34]

In addition, women with depression and anxiety utilize more health care resources, including ultrasonography, amniocentesis, and echocardiography of the infant, than do their healthy counterparts.[35,36] Hence, there is a higher chance that a cardiac malformation might be detected in an in-

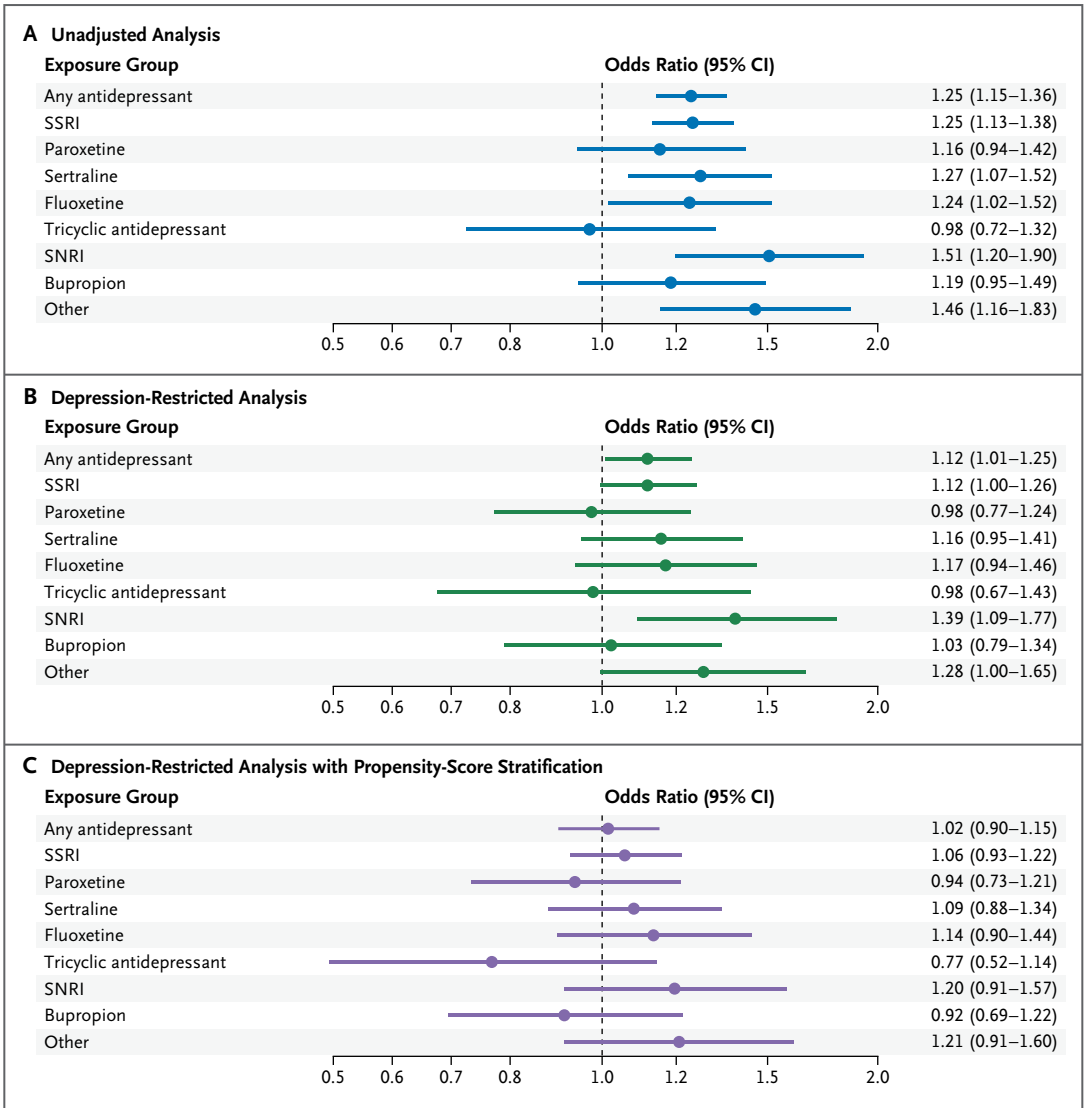

Figure 1. Risk of Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Odds ratios and 95% confidence intervals are presented to show the risk of any cardiac malformation among infants born to women with exposure to antidepressants during the first trimester, as compared with the risk among infants born to women without such exposure. Panel A shows the unadjusted analysis, Panel B the analysis restricted to women with depression, and Panel C the analysis, restricted to women with depression, that used propensity-score stratification in order to adjust for confounders. Data are from the Medicaid Analytic eXtract for the period 2000 through 2007. SNRI denotes serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.

Figure 2. Risk of Specific Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Odds ratios and 95% confidence intervals are presented to show the risk of specific cardiac malformations among infants born to women with exposure to antidepressants during the first trimester, as compared with the risk among infants born to women without such exposure. The graph shows the results of the unadjusted analysis, the analysis restricted to women with depression, and the analysis, restricted to women with depression, that used propensity-score stratification in order to adjust for confounders. Data are from the Medicaid Analytic eXtract for the period 2000 through 2007.

fant that might otherwise have been undetected clinically, particularly milder defects such as muscular ventricular septal defects, which often close during early childhood. In addition to restricting the analyses to women with a diagnosis of depression, we adjusted for a large set of prespecified and empirical potential confounding variables through the use of propensity scores. Although this approach cannot eliminate all potential confounding, it resulted in exposure groups with virtually identical measured characteristics and tended to move the risk estimates further downward.

Our crude associations were weaker than those that have been reported in some prior studies. A potential concern is the misclassification of the exposure or the outcome, since nondifferential misclassification will tend to bias results toward the null.[28] Documentation that a prescription was filled does not guarantee that the medication was actually taken as prescribed. However, secondary analyses in which we required women to have filled or refilled a prescription during the first trimester did not substantially alter the findings, although the estimates were less precise owing to the reduced cohort size.

We used validated definitions for outcomes that were based on ICD-9 coding, but a nontrivial proportion of cases were not confirmed on record review. However, an analysis that corrected the relative risk with the use of conservative estimates for the positive predictive values yielded similar results. Finally, the strength of the associations between some well-known risk factors (diabetes, use of an anticonvulsant agent, and multifetal pregnancy) and cardiac malformations that were estimated in our data set were consistent with prior reports, supporting the premise that the outcomes of interest were well captured in our study.

A strength of our study was our use of the Medicaid Analytic eXtract, which provided a very large population-based cohort, objective assessment of drug exposure, linkable clinical information, access to medical records, and availability of information on multiple pregnancy outcomes and on a wide range of potential confounders. However, our study also had some important limitations. First, the cohort included live births only. Severe cardiac malformations that resulted in spontaneous abortion, stillbirth, or termination of the pregnancy would therefore have been missed. Although this restriction could result in a bias that would underestimate the strength of the associations, our study shares this limitation with the studies that identified the potential associations, so this factor cannot explain the discrepant findings. Moreover, differences in the proportion of terminations among women with depression treated with antidepressants versus those who were not treated within the levels of covariates used in the adjustment would have to be greater than seems plausible in order to fully account for our findings (see the Supplementary Appendix).

Second, there was the potential for misclassification. Information on lifestyle factors contained in the administrative data was incomplete (e.g., smoking, obesity, and alcohol and drug abuse or dependence) or absent (e.g., body-mass index), as was information on the severity of the underlying condition (we used only proxies). However, residual confounding by such factors would be unlikely to explain the null findings; data from the National Health and Nutrition Examination Survey indicate, for example, that women of childbearing age who use antidepressants are more likely to smoke and to be obese than those who do not use these medications, with similar distributions for different antidepressants.[37]

Medicaid covers the medical expenses for more than 40% of births in the United States.[38] Medicaid-eligible pregnant women are a young, racially diverse, vulnerable population that is traditionally understudied. However, we found no evidence of effect modification according to sociodemographic characteristics. Therefore, unless there are other factors distinguishing our study cohort from other populations of pregnant women that affect the biologic relations under study, our results should be generalizable to other populations.[28]

In making decisions about whether to continue or discontinue treatment with antidepressants during pregnancy, clinicians and women must balance the potential risks of treatment with the risks of not treating severe depression.[39] In conclusion, our results suggest that the use of antidepressants during the first trimester does not substantively increase the risk of specific cardiac defects. The accumulated evidence implies low absolute risks and argues

against important cardiac teratogenic effects associated with the most commonly used antidepressant medications.

Supported by an award from the Agency for Healthcare Research and Quality (R01 HSO18533), a career development grant from the National Institute of Mental Health of the National Institutes of Health (NIH) (K01MH099141, to Dr. Huybrechts), and a training grant in reproductive, perinatal, and pediatric epidemiology from the National Institute of Child Health and Human Development of the NIH (T32HD060454, to Dr. Palmsten).

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

We thank Robert J. Glynn, Sc.D., Ph.D., for helpful comments on an earlier version of the manuscript.

REFERENCES

1. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001;323:257-60.
2. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 2008;198(2):194.e1-194.e5.
3. Mitchell A, Gilboa S, Werler M, Kelley K, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol 2011;205(1):51.e1-51.e8.
4. Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. Gen Hosp Psychiatry 2013;35:265-71.
5. FDA advising of risk of birth defects with Paxil. News release of the Food and Drug Administration, December 8, 2005 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108527.htm).
6. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate: evidence of dose relationship in teratogenic effect. CNS Drugs 2008;22:325-34.
7. Källén B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect. Reprod Toxicol 2006;21:221-2.
8. *Idem*. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 2007;79:301-8.
9. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol 2005;106:1289-96.
10. Wogelius P, Nørgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. Epidemiology 2006;17:701-4.
11. Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:1075-85.
12. Bérard A, Ramos E, Rey E, Blais L, St-André M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 2007;80:18-27.
13. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-83.
14. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:2684-92.
15. Einarson A, Pistelli A, DeSantis M, et al. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. Am J Psychiatry 2008;165:749-52. [Errata, Am J Psychiatry 2008;165:777, 1208.]
16. Wichman CL, Moore KM, Lang TR, St Sauver JL, Heise RH Jr, Watson WJ. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. Mayo Clin Proc 2009;84:23-7.
17. Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. J Clin Psychopharmacol 2012;32:186-94.
18. Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B Dev Reprod Toxicol 2008;83:68-76.
19. Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009;339:b3569.
20. Greene MF. Teratogenicity of SSRIs — serious concern or much ado about little? N Engl J Med 2007;356:2732-3.
21. Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res A Clin Mol Teratol 2010;88:159-70.
22. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to evaluate medications in pregnancy: design considerations. PLoS One 2013;8(6):e67405.
23. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernández-Díaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf 2013;22:16-24.
24. Centers for Medicare & Medicaid Services. Medicaid Analytic eXtract (MAX) general information: MAX 1999-2005 state claims anomalies (http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/MAXGeneralInformation.html).
25. Holmes LB, Westgate MN. Using ICD-9 codes to establish prevalence of malformations in newborn infants. Birth Defects Res A Clin Mol Teratol 2012;94:208-14.
26. Palmsten K, Huybrechts K, Kowal M, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf 2014 April 16 (Epub ahead of print).
27. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;154:854-64.
28. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2008.
29. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. Ann Intern Med 2002;137:693-5.
30. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.
31. O'Donnell J, Shelton R. Drug therapy of depression and anxiety disorders. In: Brunton L, Chabner B, Knollmann B, eds. Goodman & Gilman's The pharmacological basis of therapeutics 12th ed. New York: McGraw-Hill, 2011:397-416.
32. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. Int J Epidemiol 2005;34:1370-6.
33. Heart defects. In: Holmes LB. Common malformations. New York: Oxford University Press, 2012:116-26.
34. Jenkins KJ, Correa A, Feinstein JA, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovas-

cular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007;115:2995-3014.
35. Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors. Clin Ther 2007; 29:918-26.
36. Koren G. The effect of ascertainment bias in evaluating gestational antidepressant exposure. J Popul Ther Clin Pharmacol 2011;18:e174-e175.
37. Analytic and reporting guidelines: the National Health and Nutrition Examination Survey (NHANES). Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention, 2005 (http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf).
38. Garcia G. Maternal and Child Health (MCH) update: states increase eligibility for children's health in 2007. Washington, DC: National Governors Association, November 25, 2008 (http://www.nga.org/files/live/sites/NGA/files/pdf/0811MCHUPDATE.PDF;jsessionid=7B47A647247DD4E5CB9B709C8F9797AE).
39. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006;295:499-507. [Erratum, JAMA 2006; 296:170.]