

ORIGINAL ARTICLE

Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects

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ABSTRACT

BACKGROUND

Information regarding the safety of selective serotonin-reuptake inhibitors (SSRIs) in human pregnancy is sparse. Concern has been raised about the risk of congenital heart defects associated with the use of SSRIs in pregnancy.

METHODS

We obtained data on 9622 case infants with major birth defects and 4092 control infants born from 1997 through 2002 from the National Birth Defects Prevention Study. Case infants were ascertained through birth-defects surveillance systems in eight U.S. states; controls were selected randomly from the same geographic areas. Mothers completed a standardized telephone interview regarding exposure to potential risk factors, including medications, before and during pregnancy. Exposure to SSRIs was defined as treatment with any SSRI from 1 month before to 3 months after conception. Birth defects were assigned to 26 categories and subcategories.

RESULTS

There were no significant associations between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories of birth defects. Maternal SSRI use was associated with anencephaly (214 infants, 9 exposed; adjusted odds ratio, 2.4; 95% confidence interval [CI], 1.1 to 5.1), craniosynostosis (432 infants, 24 exposed; adjusted odds ratio, 2.5; 95% CI, 1.5 to 4.0), and omphalocele (181 infants, 11 exposed; adjusted odds ratio, 2.8; 95% CI, 1.3 to 5.7).

CONCLUSIONS

Maternal use of SSRIs during early pregnancy was not associated with significantly increased risks of congenital heart defects or of most other categories of birth defects. Associations were observed between SSRI use and three types of birth defects, but the absolute risks were small, and these observations require confirmation by other studies.

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THE LIFETIME RISK OF MAJOR DEPRESSION among women is 10 to 25%, with a peak prevalence during childbearing years.^{1,2} Selective serotonin-reuptake inhibitors (SSRIs) are the most frequently used class of antidepressant medications in general³ and during pregnancy.⁴ Data on the safety of SSRIs in human pregnancy are limited, but recent investigations suggest that maternal use of SSRIs during pregnancy may be associated with birth defects in general⁵⁻⁷ or with congenital heart defects in particular.^{5,7,8}

We used data from the National Birth Defects Prevention Study (NBDPS) to evaluate the relationship between maternal SSRI use in early pregnancy and the occurrence of selected birth defects.

METHODS

STUDY SUBJECTS AND DATA COLLECTION

The NBDPS is an ongoing, multisite, case-control study of environmental and genetic risk factors for more than 30 selected categories of major birth defects. Case infants had received a diagnosis of at least one selected birth defect and were ascertained by population-based birth-defects surveillance systems at eight study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas).⁹ We used data from infants who were born on or after October 1, 1997, and who had an estimated date of delivery on or before December 31, 2002. Case infants were born alive (all participating sites) or died at 20 weeks or more of gestation (Arkansas, California, Georgia, Iowa, Massachusetts, and Texas). Pregnancies with reliably ascertained defects that were electively terminated were also included in Arkansas, California, Georgia, Iowa, and Texas. Infants with recognized or strongly suspected chromosomal abnormalities or single-gene conditions were excluded from the study.

The controls were live-born infants with no major birth defects who were randomly selected from hospital or state birth-certificate records from the same geographic areas. Only one case or control infant was included from each multifetal pregnancy.

Birth defects for which at least 200 case mothers were interviewed were selected for the analysis. This number was determined as that needed to obtain 80% power with an odds ratio of 2.5, given a 2.1% exposure rate to SSRIs among control

mothers. Information on the infants in each defect category was reviewed by clinical geneticists who were unaware of the infants' exposure status, who confirmed case eligibility and classified the cases as isolated (no additional major unrelated defect) or multiple (more than one major unrelated birth defect).¹⁰ To reduce pathogenetic heterogeneity, cases with complex sequences (e.g., omphalocele-exstrophy-imperforate anus-spinal defects phenotype)¹¹ were excluded, and isolated defects were analyzed separately. A total of 709 infants who had more than one eligible birth defect were included in multiple analyses. Each case of a cardiac birth defect was reviewed by a team of experts in pediatric cardiology and the epidemiology of heart defects and was assigned to a single cardiac diagnostic category.

Demographic information and information on exposure to SSRIs and other potential risk factors during pregnancy were collected by standardized telephone interviews with mothers of case and control infants conducted in English or Spanish from 6 weeks to 2 years after the estimated date of delivery.⁹ Infants for whom complete maternal interviews were unavailable were excluded. The participation rates among case and control mothers were 71.1% and 68.6%, respectively. The mothers were asked whether they had taken any of three specific SSRIs, identified by brand name — Prozac (fluoxetine), Zoloft (sertraline), and Paxil (paroxetine) — during and before pregnancy, and when each medication was taken. They were also asked about their use of other medications during this period, which enabled us to analyze associations with other SSRIs. Exposure was defined as reported use of any SSRI from 1 month before to 3 months after conception (the date of conception was calculated as 266 days before the estimated date of delivery). Women were considered unexposed if they did not take an SSRI at any time during pregnancy or during the 3 months before conception. Women who took non-SSRI antidepressants were included in the unexposed group.

STATISTICAL ANALYSIS

Our hypothesis for this exploratory study was that SSRI exposure early in pregnancy is associated with one or more of the selected categories of birth defects. Crude analyses were performed by Pearson's chi-square test, and odds ratios and (if the expected number in a cell was less than five) Fisher's exact

confidence limits were calculated with SPSS software, version 10.0, and with SABER, with the use of the same control group for every comparison.

The following potential confounders were evaluated: maternal race or ethnic group (non-Hispanic white vs. other), maternal age (under 35 years of age vs. 35 or older), maternal education (12 years or less vs. more than 12 years), prepregnancy obesity (body-mass index [the weight in kilograms divided by the square of the height in meters] <30 vs. ≥30), maternal smoking or alcohol use from 1 month before to 3 months after conception, maternal folic acid use from 1 month before to 1 month after conception, annual family income (less than \$20,000 vs. \$20,000 or more), singleton versus multiple pregnancy, parity (no previous live births vs. one or more previous live births), and presence or absence of prepregnancy hypertension. Potential confounders were first evaluated for associations with SSRI exposure and with each of the specific defects, and they were excluded from the logistic regression if their removal resulted in a change in risk estimate of less than 10%. All confounders retained in the model for any of the defects were included in the final models for all defects. Infants of mothers with prepregnancy type 1 or 2 diabetes were excluded from adjusted analyses because of the strong association of diabetes with birth defects.

For the defects with positive associations, we performed post hoc analyses of SSRIs stratified according to factors that were associated both with maternal SSRI use and with the outcomes. These factors were maternal race or ethnic group, age, education, presence or absence of obesity, presence or absence of smoking, presence or absence of hypertension, and singleton versus multiple pregnancy. After identification of effect modification by obesity for craniosynostosis, as indicated by the Breslow–Day test, we further evaluated the effect of obesity on all defects by performing analyses with a four-level variable (obesity alone, SSRI exposure alone, both SSRI exposure and obesity, neither SSRI exposure nor obesity) by asymptotic and Fisher's exact logistic regression with the use of LogXact software, version 4.0.¹²

We also performed crude and adjusted analyses for isolated defects only and assessed the associations between four specific SSRIs (fluoxetine, sertraline, paroxetine, and citalopram [Celexa]) and 4 combined birth-defect categories and between three specific SSRIs (fluoxetine, sertraline, and

paroxetine) and 16 categories of birth defects when there were at least three exposed infants. Additional analyses were performed assessing the association between the use of any SSRI during two other time intervals of pregnancy and 16 categories of birth defects. No adjustment was made for the multiple comparisons performed.

RESULTS

Eighteen categories of birth defects and eight subcategories of cardiac birth defects met the criterion of being represented by at least 200 interviews with case mothers. Interviews were incomplete for 163 case or control mothers, and 5 mothers reported depression but did not report use of antidepressants. These subjects were excluded from the analysis, leaving 9622 case and 4092 control infants.

Of the 13,714 case and control mothers included, 408 (3.0%) reported using an SSRI at some point before or during pregnancy. The reported frequency of SSRI use in the period from 1 month before to 3 months after conception was 2.3%; 230 mothers of case infants (2.4%) and 86 mothers of control infants (2.1%) reported using an SSRI. The SSRI most commonly used by control mothers was sertraline (0.8%), followed by fluoxetine (0.7%), paroxetine (0.5%), and citalopram (0.2%).

Table 1 gives the characteristics of the case and control mothers and their reported use of SSRIs. Control mothers were significantly more likely than case mothers to be younger than 35 years of age, to have more than 12 years of education, and to have a higher family income. Case mothers were more likely than control mothers to smoke, have diabetes, have hypertension, and be obese.

For two defects, anotia or microtia and intestinal atresia, there was only one exposed case, and therefore these defects were excluded from further individual analyses. Of the 16 remaining categories and 8 subcategories, 3 showed significant associations with SSRI use: anencephaly (214 infants, 9 exposed), craniosynostosis (432 infants, 24 exposed), and omphalocele (181 infants, 11 exposed) (Table 2). Confounders that met our criteria were maternal race or ethnic group, maternal obesity, maternal smoking, and family income, and these were included in the adjusted analyses.

After post hoc analyses assessing potential effect modification by seven variables showed significant effect modification by obesity for the as-

sociation between SSRI use and craniosynostosis ($P=0.05$, by the Breslow–Day test), we performed additional exploratory analyses of effect modification by obesity for all categories of defects using a four-level variable (see Supplementary Table 1, available with the full text of this article at www.nejm.org). Among women who did not use SSRIs, obese women were more likely than nonobese women to have infants with conotruncal heart defects (adjusted odds ratio, 1.3; 95% confidence interval [CI], 1.0 to 1.6) and septal heart defects (adjusted odds ratio, 1.3; 95% CI, 1.1 to 1.5). The associations were stronger among women reporting SSRI use: for conotruncal heart defects, the adjusted odds ratio was 3.5 and the 95% CI was 1.4 to 8.7; for septal heart defects, the adjusted odds ratio was 2.8 and the 95% CI was 1.3 to 6.4. Among nonobese women, SSRI use was associated with craniosynostosis (adjusted odds ratio, 2.0; 95% CI, 1.1 to 3.7), but the risk was greater among obese women who reported SSRI use (adjusted odds ratio, 5.9; 95% CI, 2.4 to 14.3).

Restricting the analyses to infants with isolated defects resulted in wider confidence intervals and a loss of statistical significance, although there were only slight reductions in the odds ratios (see Supplementary Table 2). Restricting the exposure period to the first 2 months of pregnancy did not change the estimates appreciably (data not shown). Since the critical period for the development of craniosynostosis may extend beyond the first trimester, we examined SSRI use during the second and third trimesters and found a lower odds ratio (17 exposed; adjusted odds ratio, 1.9; 95% CI, 1.0 to 3.5). Sixteen of these women were also exposed to an SSRI during the first trimester.

In additional post hoc analyses, we assessed the associations between the use of four specific SSRIs and the risks of all 18 evaluated birth defects combined and of specific groups of birth defects (Table 3). None of the individual SSRIs were associated with significantly increased risks of all 18 birth defects combined, the 4 cardiac birth defects combined, or the 14 noncardiac birth defects combined. The use of paroxetine or citalopram significantly increased the risk of the pooled group of anencephaly, craniosynostosis, and omphalocele (Table 3).

We also assessed the association between the three most commonly used SSRIs (fluoxetine, sertraline, and paroxetine) and 16 specific cate-

gories of birth defects, but these analyses were limited by the small numbers of exposed cases for each category (see Supplementary Table 3). We found one significant association each for fluoxetine and sertraline: fluoxetine use was associated with craniosynostosis (10 exposed infants; adjusted odds ratio, 2.8; 95% CI, 1.3 to 6.1) and sertraline use with anencephaly (4 exposed infants; adjusted odds ratio, 3.2; 95% CI, 1.1 to 9.3). We found four significant associations for paroxetine: with anencephaly (five exposed infants; adjusted odds ratio, 5.1; 95% CI, 1.7 to 15.3), right ventricular outflow tract obstruction defects (seven exposed infants; adjusted odds ratio, 2.5; 95% CI, 1.0 to 6.0), omphalocele (six exposed infants; adjusted odds ratio, 8.1; 95% CI, 3.1 to 20.8), and gastroschisis (five exposed infants; adjusted odds ratio, 2.9; 95% CI, 1.0 to 8.4). None of the mothers of case infants with defects found to be associated with SSRI use were concomitantly exposed to medications with a known teratogenic effect.

DISCUSSION

Using data from a population-based case–control study, we found no significant associations between the use of SSRIs in early pregnancy and the risks of the majority of birth defects assessed in this study, including congenital heart defects. However, we observed associations between SSRI use and the occurrence of anencephaly, craniosynostosis, and omphalocele, defects that had not been previously associated with maternal SSRI use in pregnancy.

Studies in animals have demonstrated delayed ossification in offspring after maternal treatment with sertraline.^{13,14} A specific role of serotonin in cardiac and craniofacial morphogenesis in the rodent embryo has also been established.^{15–17} Several recent reports have suggested possible associations between maternal use of paroxetine during pregnancy and birth defects in humans. A report from the Swedish Medical Birth Register showed an increased risk of heart defects overall, and of ventricular and atrial septal defects specifically, among infants whose mothers took paroxetine (but not other SSRIs).¹⁸ That report did not find the associations we observed between SSRI use and craniosynostosis or abdominal wall defects (omphalocele and gastroschisis were not examined separately).

Table 1. Characteristics of Mothers of Case and Control Infants.*			
Characteristic	Mothers of Case Infants (N=9622)	Mothers of Control Infants (N=4092)	P Value†
	<i>no./total no. (%)</i>		
Race or ethnic group‡			0.01
Non-Hispanic white	5861/9603 (61.0)	2454/4081 (60.1)	
Non-Hispanic black	978/9603 (10.2)	491/4081 (12.0)	
Hispanic	2238/9603 (23.3)	931/4081 (22.8)	
Other	526/9603 (5.5)	205/4081 (5.0)	
Age			0.003
<35 yr	8057/9622 (83.7)	3508/4092 (85.7)	
≥35 yr	1565/9622 (16.3)	584/4092 (14.3)	
Education			0.003
≤12 yr	4278/9613 (44.5)	1705/4084 (41.7)	
>12 yr	5335/9613 (55.5)	2379/4084 (58.3)	
Prepregnancy BMI§			<0.001
<18.5	565/9265 (6.1)	233/3931 (5.9)	
18.5–24.9	4975/9265 (53.7)	2253/3931 (57.3)	
25.0–29.9	2058/9265 (22.2)	861/3931 (21.9)	
≥30.0	1667/9265 (18.0)	584/3931 (14.9)	
Cigarette smoking¶			0.005
0/day	7488/9612 (77.9)	3294/4087 (80.6)	
1–14/day	1721/9612 (17.9)	646/4087 (15.8)	
15–24/day	335/9612 (3.5)	126/4087 (3.1)	
≥25/day	68/9612 (0.7)	21/4087 (0.5)	
Annual family income			0.05
<\$20,000	2923/8750 (33.4)	1115/3564 (31.3)	
\$20,000–\$49,999	2845/8750 (32.5)	1167/3564 (32.7)	
≥\$50,000	2982/8750 (34.1)	1282/3564 (36.0)	
Prepregnancy type 1 or 2 diabetes			<0.001
No	8691/8884 (97.8)	3833/3854 (99.5)	
Yes	193/8884 (2.2)	21/3854 (0.5)	
Prepregnancy hypertension			0.009
No	8093/9479 (85.4)	3558/4086 (87.1)	
Yes	1386/9479 (14.6)	528/4086 (12.9)	
Alcohol use¶¶			0.84
No	5899/9622 (61.3)	2501/4092 (61.1)	
Yes	3723/9622 (38.7)	1591/4092 (38.9)	
Folic acid use 			0.98
No	4832/9622 (50.2)	2056/4092 (50.2)	
Yes	4790/9622 (49.8)	2036/4092 (49.8)	
Singleton vs. multiple pregnancy			<0.001
Singleton	8996/9606 (93.6)	3957/4087 (96.8)	
Multiple	610/9606 (6.4)	130/4087 (3.2)	

Table 1. (Continued.)

Characteristic	Mothers of Case Infants (N=9622)	Mothers of Control Infants (N=4092)	P Value†
	no./total no. (%)		
Parity			<0.001
0 Previous live births	4171/9619 (43.4)	1635/4090 (40.0)	
≥1	5448/9619 (56.6)	2455/4090 (60.0)	
Exposure to SSRIs**			0.30
No	9320/9550 (97.6)	3979/4065 (97.9)	
Yes	230/9550 (2.4)	86/4065 (2.1)	
Exposure to non-SSRI antidepressants**			0.08
No	9229/9302 (99.2)	3954/3974 (99.5)	
Yes	73/9302 (0.8)	20/3974 (0.5)	
Time from expected due date to interview			<0.001
<1 yr	6127/9603 (63.8)	3216/4077 (78.9)	
≥1 yr	3476/9603 (36.2)	861/4077 (21.1)	

* Data are taken from the National Birth Defects Prevention Study for the period from 1997 through 2002.

† P values were calculated by Pearson's chi-square test.

‡ Race or ethnic group was self-assessed.

§ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. BMI values of less than 18.5, 18.5 to 24.9, 25.0 to 29.9, and 30 or more represent underweight, normal weight, overweight, and obesity, respectively.

¶ Smoking and alcohol use are reported for the period from 1 month before to 3 months after conception.

|| Folic acid use is reported for the period from 1 month before to 1 month after conception.

** Exposure was defined as reported use of any SSRI from 1 month before to 3 months after conception. Women were considered not to have been exposed if they did not take an SSRI at any time during pregnancy or during the 3 months before conception. Women who took non-SSRI antidepressants were included in the unexposed group.

An unpublished analysis of administrative records from a managed care organization showed an increased risk of major birth defects overall, and of heart defects specifically, among infants whose mothers received prescriptions for paroxetine as compared with those whose mothers received prescriptions for other antidepressants during pregnancy.⁵ Similar results were shown in another unpublished cohort study among women treated with paroxetine during the first trimester as compared with women who did not take SSRIs.¹⁹ A cohort study based on administrative data from Quebec, Canada, showed that the risks of major birth defects and of heart defects were greater among infants whose mothers took high doses of paroxetine during early pregnancy than among those whose mothers took non-SSRI antidepressants, but this association was not seen among infants whose mothers took lower doses of paroxetine.⁷

In a Finnish cohort study, the overall risk of major malformations was not significantly increased among infants born to women treated

with fluoxetine during the first trimester, but an increase in the risk of heart defects by a factor of three was noted.²⁰ A Danish cohort study showed an increased risk of congenital malformations in general among women given prescriptions for any SSRI.⁶ Other epidemiologic studies have not shown a significant association between major birth defects and maternal SSRI use during pregnancy.²¹⁻²⁵ However, all previous studies have had limitations, such as insufficient power, issues with ascertainment or classification of birth defects, inability to address potential confounding, or poor information on exposure.

Some, but not all, of our findings are consistent with those of another large case-control study in this issue of the *Journal*.²⁶ Like our report, that study showed no significant associations between SSRI use overall and congenital heart defects. It did show significant associations between paroxetine use and right ventricular outflow tract obstruction defects (six infants; adjusted odds ratio, 3.3; 95% CI, 1.3 to 8.8) and neural-tube defects (four infants; adjusted odds ratio, 3.3; 95% CI, 1.1 to 10.4;

Table 2. Associations between Maternal Use of Any SSRI and Major Birth Defects.*

Birth Defect	No. of Infants	No. Exposed	Crude Analysis	Adjusted Analysis†	
			Odds Ratio (95% CI)	Odds Ratio (95% CI)	P Value
No major defects (control infants)	4092	83			
Anencephaly	214	9	2.0 (1.0–4.3)	2.4 (1.1–5.1)	0.02
Spina bifida	457	7	0.7 (0.3–1.6)	0.7 (0.3–1.7)	0.47
Anotia or microtia	253	1			
Conotruncal heart defects	977	25	1.3 (0.8–2.1)	1.3 (0.8–2.1)	0.19
Transposition of the great arteries	309	9	1.4 (0.7–3.0)	1.4 (0.7–3.0)	0.27
Tetralogy of Fallot	428	10	1.2 (0.6–2.3)	1.2 (0.6–2.5)	0.47
Septal heart defects	1931	43	1.1 (0.7–1.7)	1.1 (0.7–1.6)	0.51
Perimembranous ventricular septal defect	797	18	1.1 (0.6–1.9)	1.2 (0.7–1.9)	0.57
Atrial septal defect — ostium secundum	768	17	1.1 (0.6–1.9)	1.1 (0.6–1.8)	0.76
Atrial septal defect — not otherwise specified	252	5	1.0 (0.3–2.4)	1.0 (0.4–2.5)	0.99
Right ventricular outflow tract obstruction defects	669	16	1.2 (0.7–2.0)	1.3 (0.7–2.2)	0.38
Pulmonary-valve stenosis	480	12	1.3 (0.6–2.3)	1.3 (0.7–2.4)	0.38
Left ventricular outflow tract obstruction defects	691	14	1.0 (0.5–1.8)	0.9 (0.5–1.7)	0.82
Hypoplastic left heart	218	3	0.6 (0.2–2.2)	0.6 (0.2–2.1)	0.50
Coarctation of aorta	358	7	1.0 (0.3–2.1)	0.8 (0.3–2.0)	0.74
Cleft lip with or without cleft palate	1127	22	1.0 (0.6–1.6)	0.8 (0.5–1.4)	0.63
Cleft palate alone	620	11	0.9 (0.4–1.7)	0.8 (0.4–1.5)	0.56
Esophageal atresia	300	9	1.5 (0.7–3.0)	1.3 (0.6–2.7)	0.48
Intestinal atresia	262	1			
Anorectal atresia	418	8	1.0 (0.4–2.0)	0.7 (0.3–1.8)	0.53
Hypospadias, 2nd or 3rd degree	823	14	0.8 (0.4–1.5)	0.7 (0.4–1.4)	0.32
Transverse limb deficiencies	346	8	1.1 (0.5–2.4)	1.2 (0.6–2.6)	0.55
Craniosynostosis	432	24	2.8 (1.7–4.5)	2.5 (1.5–4.0)	<0.001
Omphalocele	181	11	3.2 (1.6–6.1)	2.8 (1.3–5.7)	0.005
Diaphragmatic hernia	297	10	1.7 (0.8–3.3)	1.6 (0.8–3.3)	0.18
Gastroschisis	413	11	1.3 (0.7–2.5)	1.3 (0.6–2.6)	0.42

* SSRI use is reported for the period from 1 month before to 3 months after conception. Eighteen categories of birth defects and eight subcategories of cardiac birth defects are listed. Analyses were performed for categories for which there were at least three exposed infants. Data are taken from the National Birth Defects Prevention Study for the period from 1997 through 2002. SSRI denotes selective serotonin-reuptake inhibitor, and CI confidence interval.

† Odds ratios are adjusted for maternal race or ethnic group, presence or absence of maternal obesity, presence or absence of maternal smoking, and family income. Infants whose mothers had prepregnancy type 1 or 2 diabetes mellitus are excluded.

anencephaly and spina bifida were not examined separately). However, that report found no significant association between craniosynostosis and SSRI use, and for omphalocele it found a significant association only with sertraline.

Our study is population-based and includes a large birth sample, allowing the evaluation of the relationship between SSRI use and specific types

of birth defects. The study also uses careful case definitions and review and excludes infants with chromosomal abnormalities and single-gene disorders. Although the large size of our study overall allowed for consideration of several potential confounders and effect modifiers, the small number of exposed infants for each individual defect remains a limitation.

Table 3. Associations between Maternal Use of Specific SSRIs and Pooled Birth-Defect Categories.*

Category	Fluoxetine		Sertraline		Paroxetine		Citalopram	
	No. Exposed	Adjusted Odds Ratio (95% CI)	No. Exposed	Adjusted Odds Ratio (95% CI)	No. Exposed	Adjusted Odds Ratio (95% CI)	No. Exposed	Adjusted Odds Ratio (95% CI)
No major defects (control infants)	29		32		18		7	
18 Birth defects pooled	76	1.1 (0.7–1.7)	68	0.9 (0.6–1.4)	70	1.6 (0.9–2.7)	22	1.2 (0.5–2.8)
4 Cardiac birth defects†	33	1.2 (0.7–2.1)	22	0.7 (0.4–1.3)	32	1.7 (0.9–3.1)	11	1.5 (0.6–4.0)
14 Noncardiac birth defects‡	47	1.1 (0.7–1.7)	51	1.0 (0.6–1.6)	42	1.5 (0.9–2.7)	12	1.0 (0.4–2.5)
3 Birth defects previously identified as associated with SSRI use§	13	1.9 (1.0–4.0)	13	2.0 (1.0–3.9)	16	4.2 (2.1–8.5)	6	4.0 (1.3–11.9)

* Data are taken from the National Birth Defects Prevention Study for the period from 1997 through 2002. Odds ratios are adjusted for maternal race or ethnic group, presence or absence of maternal obesity, presence or absence of maternal smoking, and family income. Infants whose mothers had prepregnancy type 1 or 2 diabetes are excluded. Cases with at least one cardiac birth defect and at least one noncardiac birth defect have been included in both categories. SSRI denotes selective serotonin-reuptake inhibitor, and CI confidence interval.

† The four cardiac birth defects are conotruncal, septal, right ventricular outflow tract obstruction, and left ventricular outflow tract obstruction defects.

‡ The 14 noncardiac birth defects are anencephaly, spina bifida, anotia or microtia, cleft lip with or without cleft palate, cleft palate alone, esophageal atresia, intestinal atresia, anorectal atresia, second or third degree hypospadias, transverse limb deficiencies, craniosynostosis, omphalocele, diaphragmatic hernia, and gastroschisis.

§ These three birth defects are anencephaly, craniosynostosis, and omphalocele.

Because of the large number of comparisons evaluated in our analysis, it is likely that some of the observed associations reflect chance variation. We performed a total of 265 tests, with 54 positive results at the 0.05 significance level; we would have expected 14 positive results to occur by chance. Not all positive tests are reported, and it is not possible to identify which, if any, of the observed associations are due to chance alone. Analyses of other data sets are warranted to replicate our findings.

The effect modification by prepregnancy obesity that we observed post hoc for the association between SSRI use and the occurrence of some birth defects has not, to our knowledge, been reported previously, and confirmation is needed. However, maternal obesity itself has been associated with increased risks of neural-tube defects,^{27,28} congenital heart defects,^{27,29} and other defects.^{27,30} The effect modification we observed may reflect differences in the pharmacokinetics of these lipophilic drugs in women with various percentages of body fat.³¹

An important limitation of this study is our inability to separate the effect of maternal SSRI use from that of the underlying depression. Only 39 case or control mothers reported having had depression when asked a general question about illnesses during pregnancy. All but five of these women reported taking an antidepressant medi-

cation before or during pregnancy. Data on dosage were unavailable, so that analysis of dose-response relationships could not be performed. When they were questioned about the use of medications, the mothers were prompted by brand names for the three most commonly used SSRIs, leading to potential underreporting of other SSRIs. Exposures were determined by maternal report, which introduces a potential for recall bias. Selection bias may have occurred, because participation was less than 100%; however, it is unlikely that participation varied according to SSRI exposure status, and therefore any selection bias was probably in favor of the null hypothesis.

Our study did not show an increased risk of most birth defects, and SSRI exposure was present in only a small number of cases of certain defects. The absolute risks associated with SSRIs appear small in comparison with the baseline risks of birth defects that exist in every pregnancy. Maternal stress and depression during pregnancy have been associated with adverse reproductive outcomes,^{32,33} and discontinuation of antidepressant treatment in pregnant women with serious depressive illness may have adverse effects on the mother and her baby.³⁴ Thorough assessment of the potential risks and benefits of SSRI use is necessary to allow women of reproductive age to make informed decisions about such therapy.

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The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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