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Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects

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IMPORTANCE Antidepressants are commonly used during pregnancy, but limited information is available about individual antidepressants and specific birth defect risks.

OBJECTIVE To examine associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions.

DESIGN, SETTING, AND PARTICIPANTS The population-based, multicenter case-control National Birth Defects Prevention Study (October 1997–December 2011) included cases with selected birth defects who were identified from surveillance systems; controls were randomly sampled live-born infants without major birth defects. Mothers of cases and controls participated in an interview after the expected delivery date. The data were analyzed after the completion of the National Birth Defects Prevent Study's data collection.

EXPOSURES Self-reported antidepressant exposure was coded to indicate monotherapy exposure to antidepressants.

MAIN OUTCOMES AND MEASURES We used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals for associations between maternal antidepressant use and birth defects. We compared early pregnancy antidepressant-exposed women with those without antidepressant exposure and, to partially account for confounding by underlying maternal conditions, those exposed to antidepressants outside of the birth defect development critical period.

RESULTS This study included 30 630 case mothers of infants with birth defects and 11 478 control mothers (aged 12–53 years). Early pregnancy antidepressant use was reported by 1562 case mothers (5.1%) and 467 control mothers (4.1%), for whom elevated aORs were observed for individual selective serotonin reuptake inhibitors (SSRIs) and selected congenital heart defects (CHD) (eg, fluoxetine and anomalous pulmonary venous return: aOR, 2.56; 95% CI, 1.10-5.93; this association was attenuated after partially accounting for underlying conditions: aOR, 1.89; 95% CI, 0.56-6.42). This pattern was observed for many SSRI-CHD combinations. Associations between SSRIs and non-CHD birth defects often persisted or strengthened after partially accounting for underlying conditions (eg, citalopram and diaphragmatic hernia: aOR, 5.11; 95% CI, 1.29-20.24). Venlafaxine had elevated associations with multiple defects that persisted after partially accounting for underlying conditions (eg, anencephaly and craniorachischisis: aOR, 9.14; 95% CI, 1.91-43.83).

CONCLUSIONS AND RELEVANCE We found some associations between maternal antidepressant use and specific birth defects. Venlafaxine was associated with the highest number of defects, which needs confirmation given the limited literature on venlafaxine use during pregnancy and risk for birth defects. Our results suggest confounding by underlying conditions should be considered when assessing risk. Fully informed treatment decision-making requires balancing the risks and benefits of proposed interventions against those of untreated depression or anxiety.

Editorial

Supplemental content

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Depressive and anxiety disorders affect 7.1% and 19.1%, respectively, of the US adult population annually and disproportionately affect reproductive-aged women.[1] Antidepressants and evidence-supported psychotherapies are first-line treatment options for most depressive and anxiety disorders.[2-5] Approximately 10% to 15% of US reproductive-aged women are prescribed antidepressants annually.[6,7] These disorders are prevalent among pregnant women,[8] with 6% to 8% of US pregnant women reporting being prescribed or using an antidepressant.[9-12]

Managing these disorders during pregnancy and the postpartum period remains challenging,[13,14] but effective management can maintain maternal and infant health,[15] improve maternal prenatal health care practices,[16] and improve maternal-infant attachment.[17] However, concerns remain about the adverse associations of antidepressants with fetal and infant health,[18,19] including birth defect risk after early pregnancy exposure.[20,21] Research examining the associations between antidepressant use during pregnancy and infant health, while accounting for the underlying maternal condition, is needed to inform evidence-based guidance for clinical management before and during pregnancy.[20,22,23]

Some antidepressants may be associated with an increased risk for birth defects or congenital heart defects overall,[20,24-27] although findings are occasionally mixed. Fewer studies have examined the associations between individual antidepressants and specific birth defects, which are critical as teratogens rarely increase risks for all defects.[28,29] Most analyses have focused on selective serotonin reuptake inhibitors (SSRIs),[30-36] with limited studies on other first-line antidepressants, such as serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion. The clinical usefulness of prior research is limited by the inability to account for associations between the underlying condition and birth defects, which may confound associations between early pregnancy antidepressant use and birth defect risk[33,37] and possibly yield inaccurate risk estimates. Building on interim data from the National Birth Defects Prevention Study (NBDPS),[38-42] we present final NBDPS data on associations between antidepressant use during early pregnancy and specific birth defects. Given increased sample size, we examine associations between more antidepressants and birth defects and account, at least partially, for potential confounding by underlying conditions and environmental factors.

Key Points

Question Which antidepressants used by pregnant women are associated with specific birth defects and do associations between antidepressants and specific birth defects remain after partially accounting for the underlying condition?

Findings In this case-control study of 30 630 mothers of infants with birth defects and 11 478 control mothers, there were previous and new associations between individual selective serotonin reuptake inhibitors, venlafaxine, and bupropion and specific birth defects. Many selective serotonin reuptake inhibitor and birth defect (particularly heart defect) associations attenuated after partially accounting for the underlying condition; most venlafaxine associations remained.

Meaning Venlafaxine was associated with more birth defects than other antidepressants, which needs confirmation; studies to assess birth defect risk among women taking antidepressants should account for the underlying condition.

Methods

Participants and Procedures

The NBDPS was a US population-based, multisite (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) case-control study that examined risk factors for major structural birth defects.[43] Cases with selected birth defects (a full list of eligible defects is available[43]) were identified from surveillance systems using standard case definitions and included live births (all sites), stillbirths (all sites but New York before 2000 and New Jersey), and terminations (all sites except Georgia before 1999, Massachusetts before 2011, New York before 2000, and New Jersey).[43] Clinical data were abstracted from medical records and classified by clinician geneticists and other clinicians.[43-45] Sites collected data on pregnancies ending on or after October 1, 1997, through those with an estimated date of delivery (EDD) on or before December 31, 2011. Infants with known single-gene disorders or chromosomal abnormalities were excluded. Controls were randomly sampled live-born infants without major birth defects identified via vital records or hospital birth logs from the same birth months and state- or county-level (depending on the site) geographic catchment area as cases.[43] Mothers participated in a computer-assisted telephone interview 6 weeks to 24 months after the EDD, with a median time to interview of 11 months for case and 9 months for control mothers (67% case and 65% control mother participation, respectively). Institutional review board approval was provided by all sites and mothers gave oral interview informed consent.

Mothers were asked about the use of citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, and bupropion during the 3 months before conception or during pregnancy; specific probing for citalopram and venlafaxine began with EDDs in 2006. Other antidepressants could be reported when women were asked to report any medications used, as well as any disease and subsequent medication treatment in the 3 months before or during pregnancy. Mothers were not asked specifically about depressive or anxiety diagnoses. Mothers were asked start and stop dates, duration, and frequency of medication use. Timing before or during pregnancy was calculated using pregnancy months (consecutive 30-day intervals from the estimated conception date to delivery/end of pregnancy). Medications were coded using the Slone Drug Dictionary (Boston University), which links medication products to corresponding active components. We identified antidepressants in the following classes: SSRI, SNRI, tricyclic antidepressants and other norepinephrine reuptake inhibitor, monoamine oxidase inhibitor, and other antidepressants (eTable 1 in the Supplement). Early pregnancy exposure was defined as maternal report of using 1 or

more medication product(s) in these classes in any dose, duration, or frequency from the month before conception through the third pregnancy month; the month before conception was included in early pregnancy estimates to account for the imprecision of conception date estimates and medication exposure dates. Early pregnancy antidepressant use was coded to indicate component (eg, sertraline only) or class-level (eg, SSRIs only) monotherapy exposure; if multiple antidepressants were used, women were coded as such. Women were considered unexposed if they reported no antidepressant use during the 3 months before conception through their pregnancy's end. Women were considered exposed only outside of early pregnancy if they reported exposure to any antidepressant, but solely during the 2 to 3 months before conception and/or pregnancy months 4 to 9.

Statistical Analysis

The NBDPS included 32 200 case and 11 829 control mothers. Mothers were excluded from this analysis if they had incomplete medication history (797 [1.8%]), prepregnancy type 1 or 2 diabetes (830 [1.9%]), or used a known teratogenic medication during the 3 months before conception or during pregnancy (215 [0.5%]). Mothers were excluded if they, without prompting, reported having a depressive, bipolar, or anxiety disorder but did not report antidepressant use (79 [0.2%]). There were 30 630 case and 11 478 control mothers included in our analysis.

We estimated the prevalence of early pregnancy use of each antidepressant and broader medication class for case and control mothers separately. For antidepressants taken as monotherapy with a 0.2% or greater prevalence among control mothers in early pregnancy, we examined the time trends for each antidepressant in 2-year increments. We used χ^2 tests to examine the distributions of characteristics among control mothers with any early pregnancy monotherapy or polytherapy antidepressant exposure compared with (1) unexposed control mothers and (2) control mothers whose only exposure to an antidepressant(s) occurred outside of early pregnancy. For specific antidepressants with a 0.2% or greater monotherapy exposure prevalence among control mothers during early pregnancy, we examined percentage distributions among these antidepressants used in monotherapy by selected maternal characteristics.

To identify associations between early pregnancy antidepressant use and specific birth defects, we used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals for NBDPS-eligible birth defects with 4 or more exposed cases. We tested 2 model sets: (1) mothers exposed to each antidepressant during early pregnancy compared with mothers unexposed to an antidepressant before or during pregnancy and (2) mothers who were exposed to each antidepressant during early pregnancy compared with mothers only exposed to an antidepressant(s) outside of early pregnancy. The approach used in set 2 was intended to account partially for confounding by the underlying condition. That is, women exposed only outside of early pregnancy may have had similar conditions, as well as other factors associated with these conditions, during and around the time of pregnancy but did not take antidepressants during the birth defect critical period. In this analysis, the phrase *underlying condition* is intended to describe the condition necessitating treatment with an antidepressant as well as social and environmental factors associated with the condition. In set 2, one would expect to see elevated aORs for associations between the antidepressant and specific birth defects if the antidepressant was associated with the outcome, as the underlying condition and its corollaries would be taken at least partially into account given the analytic strategy. Covariates with known associations with birth defects were tested for inclusion in model sets 1 and 2 by assessing statistical differences for each covariate between the early pregnancy antidepressant-exposed group and both comparison groups in line with a common cause covariate selection approach.[46] In final models, covariates were included if they resulted in a 10% or greater change in any point estimate for associations between the exposure and any defects tested.[46,47] Covariates were consistent within a model set, but may have differed between sets based on the previously described criteria. We examined individual antidepressants and classes with 0.2% or greater early pregnancy antidepressant monotherapy prevalence among control mothers. Except for analyses examining any antidepressant or multiple medication class use, monotherapy use of individual antidepressants or of specific classes in early pregnancy was examined. We had substantial power to detect small to moderate effect sizes for many associations; the power to detect rarer birth defects was limited given smaller control-case ratios,[48] especially for the confounding by underlying condition analyses. Given this, and to align with American Statistical Association guidelines to consider effect sizes when interpreting results instead of statistical significance,[49] we noted associations as meaningfully elevated if aORs were 2.0 or greater and lower confidence interval bounds were 0.8 or greater. Analyses were conducted with SAS, version 9.4 (SAS Institute).

Results

Early pregnancy antidepressant use was reported by 1562 cases (5.1%) and 467 control mothers (4.1%; **Table 1**); among control mothers, the most common (≥0.2% monotherapy prevalence) antidepressants were sertraline, fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, and bupropion. Sertraline, fluoxetine, citalopram, and escitalopram use during early pregnancy increased over the study years (**Figure**). Compared with unexposed control mothers, early pregnancy antidepressant-exposed control mothers were more likely to be older, non-Hispanic white, have higher levels of education, have a higher prepregnancy body mass index (calculated as weight in kilograms divided by height in meters squared), report early pregnancy smoking or alcohol use, periconceptional folic acid use, and have a previous live birth (**Table 2**). Compared with control mothers only exposed to an antidepressant outside of early pregnancy, early pregnancy antidepressant-exposed control mothers had higher levels of education. The characteristics of control mothers who used each antidepressant during early pregnancy are in Table 2.

Table 1. Antidepressant Medication Use Prevalence Among US Women Before and During Pregnancy in the National Birth Defects Prevention Study From 1997 to 2011

Antidepressant medication use	NBDPS participant, No. (%)	
	Case (n = 30 630)	Control (n = 11 478)
No antidepressant use before or during pregnancy[a]	28 719 (93.8)	10 886 (94.8)
Any antidepressant use		
Only outside of early pregnancy[b]	349 (1.1)	125 (1.1)
Reported in early pregnancy[c]	1562 (5.1)	467 (4.1)
Early pregnancy SSRIs only[d]	1108 (3.6)	341 (3.0)
Monotherapy		
Citalopram	126 (0.4)	39 (0.3)
Escitalopram	102 (0.3)	35 (0.3)
Fluoxetine	275 (0.9)	81 (0.7)
Fluvoxamine	2 (0.0)	1 (0.0)
Paroxetine	166 (0.5)	43 (0.4)
Sertraline	390 (1.3)	129 (1.1)
SSRI only polytherapy[e]	47 (0.2)	13 (0.1)
Early pregnancy SNRIs only[d]	138 (0.5)	27 (0.2)
Monotherapy		
Desvenlafaxine	4 (0.0)	2 (0.0)
Duloxetine	22 (0.1)	4 (0.0)
Venlafaxine	112 (0.4)	21 (0.2)
Early pregnancy TCA-NEs only[d]	29 (0.1)	15 (0.1)
Monotherapy		
Amitriptyline	17 (0.1)	7 (0.1)
Clomipramine	1 (0.0)	0 (0.0)
Desipramine	1 (0.0)	0 (0.0)
Doxepin	0 (0.0)	3 (0.0)
Imipramine	2 (0.0)	2 (0.0)
Nortriptyline	8 (0.0)	3 (0.0)
Early pregnancy other antidepressant use only[d]	174 (0.6)	54 (0.5)
Monotherapy		
Bupropion	149 (0.5)	45 (0.4)
Mirtazapine	2 (0.0)	4 (0.0)
Nefazodone	3 (0.0)	3 (0.0)
Trazodone	18 (0.1)	2 (0.0)
Other antidepressant only polytherapy[f]	2 (0.0)	0 (0.0)
Early pregnancy multiple antidepressant class use[d]	113 (0.4)	30 (0.3)
Any SSRI and bupropion only	40 (0.1)	16 (0.1)
Any SNRI and bupropion only	10 (0.0)	4 (0.0)
Any SSRI and any SNRI only	15 (0.0)	2 (0.0)
Any other combination of multiple classes[g]	48 (0.2)	8 (0.1)

Abbreviations: NBDPS, National Birth Defects Prevention Study; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA-NE, tricyclic and norepinephrine reuptake inhibitors.

[a] Three months before conception through the end of pregnancy.

[b] Two or 3 months before conception and/or during the fourth to ninth months of pregnancy.

[c] One month before conception through the third month of pregnancy.

[d] Women who reported only taking antidepressant medication(s) in the specific class in the month before through the third month of pregnancy were included in specific antidepressant class and medication counts. Women who reported taking an antidepressant from more than 1 class in the month before through the third month of pregnancy were included in the early pregnancy multiple antidepressant class use category.

[e] Among women who reported using multiple SSRIs in the month before through the third pregnancy month, the most common combinations among case mothers were fluoxetine and paroxetine (12 [25.5%]) and paroxetine and sertraline (11 [23.4%]). The most common combination among control mothers was paroxetine and sertraline (6 [46.2%]).

[f] Both case mothers who reported using multiple other antidepressants in the month before conception through the third pregnancy month used bupropion and trazodone.

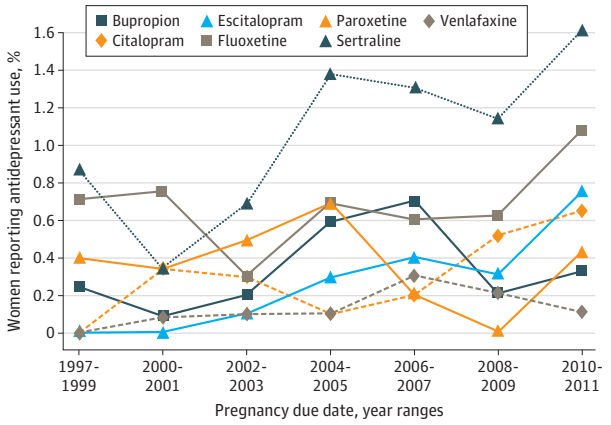
[g] Among case mothers who reported any other combination of multiple classes, 11 reported use of an SSRI and a TCA, 19 reported use of an SSRI and an "other" antidepressant (not including bupropion), 5 reported use of an SNRI and an "other" antidepressant (not including bupropion), 1 reported using a TCA and another antidepressant, and 12 reported using 3 or more medications across 2 or more classes. Among control mothers who reported any other combination of multiple classes, 1 reported an SSRI and a TCA, 2 reported using an SSRI and another antidepressant (not including bupropion), 1 reported using an SNRI and an "other" antidepressant (not including bupropion), and 4 reported using 3 or more medications across 2 or more classes.

In set 1 of the birth defect analyses, which compared early pregnancy antidepressant-exposed women with women unexposed to antidepressants before and during pregnancy, models were adjusted for maternal race/ethnicity, prepregnancy body mass index, education, and early pregnancy smoking and alcohol use. Mothers who used paroxetine or fluoxetine in early pregnancy had the highest proportion of elevated aORs with specific birth defects among the SSRIs examined, followed by citalopram and sertraline (eTable 2 and eFigures 1-5 in the Supplement). There were no elevated aORs between escitalopram and specific birth defects. Mothers who used venlafaxine had elevated aORs for most examined defects; some were relatively high (ie, aORs 3.34 [95% CI, 1.69-6.60]-5.26 [95% CI, 1.96-14.12]) (eTable 2 and eFigure 6 in the Supplement). We observed elevated aORs between bupropion and 3 defects (eTable 2 and eFigure 7 in the Supplement). The results for the associations between antidepressant classes and birth defects are in eTable 3 in the Supplement.

In set 2 of the birth defect analyses, which compared early pregnancy antidepressant-exposed women with women exposed only to an antidepressant outside of early pregnancy, models were adjusted for maternal education. Many of the previously elevated aORs for the 5 SSRIs and heart defects were attenuated (eTable 2 vs eTable 4 and eFigures 1-5 in the Supplement; for example, fluoxetine and anomalous pulmonary venous return [aOR, 2.56; 95% CI, 1.10-5.93; this association was attenuated after partially accounting for the underlying condition: aOR, 1.89; 95% CI, 0.56-6.42]). Although this pattern of attenuation after accounting for the underlying condition was observed for many SSRI and CHD combinations, there were 2 exceptions: fluoxetine with coarctation of the aorta (aOR, 2.06; 95% CI, 0.89-4.74) and citalopram with atrioventricular

septal defect (aOR, 3.73; 95% CI, 0.86-16.27). After at least partially accounting for the underlying condition, we observed elevated aORs for specific SSRIs and nonheart defects, including sertraline and diaphragmatic hernia (aOR, 2.72; 95% CI, 0.84-8.81); fluoxetine and esophageal atresia (aOR, 2.61; 95% CI, 0.98-6.93); paroxetine and anencephaly and craniorachischisis (aOR, 3.43; 95% CI, 0.99-11.82); paroxetine and gastroschisis (aOR, 2.11; 95% CI, 0.97-4.59); and citalopram and diaphragmatic hernia (aOR, 5.11; 95% CI, 1.29-20.24) (eTable 4 and eFigures 1-4 in the Supplement). There were no elevated aORs between escitalopram and the examined defects. After accounting for the underlying condition, the elevated venlafaxine aORs persisted for most defects; in some instances, the association strength increased (anencephaly and craniorachischisis [aOR, 9.14; 95% CI, 1.91-43.83]; eTable 4 and eFigure 6 in the Supplement). To test the robustness of these findings, we split the NBDPS data into previously reported (1997-2007)[41] and new (2008-2011). Venlafaxine was associated with many of the same defects across the samples (data not shown). After accounting for the underlying condition, we observed an elevated aOR for bupropion and diaphragmatic hernia (aOR, 6.50; 95% CI, 1.85-22.88) (eTable 4 and eFigure 7 in the Supplement). Antidepressant class and birth defect association results, after accounting for the underlying condition, are in eTable 5 in the Supplement. To assess whether attenuations or increases in the aORs were because of using a different set of covariates in the second set (vs set 1) of the birth defect analyses, we also ran a sensitivity analysis controlling for the same covariates used in model set 1. The observed associations between early pregnancy antidepressant use and specific birth defects, after accounting at least partially for the underlying condition, were largely similar in the main analysis (eTable 4 in the Supplement) and the sensitivity analysis (eTable 6 in the Supplement).

Figure. Early Pregnancy Monotherapy Antidepressant Use Over Time Among Control Mothers in the National Birth Defects Prevention Study From 1997 to 2011



Discussion

We found several previously reported associations between individual antidepressants and specific birth defects and extended prior research by identifying associations that, to our knowledge, have not been previously reported or examined. Comparing early pregnancy exposed mothers with mothers exposed to antidepressants only outside of early pregnancy (the birth defect development critical period) attenuated estimates for many specific SSRI and heart defect associations. This attenuation was not observed for many specific SSRI and nonheart birth defect associations, as well as associations between venlafaxine and heart or nonheart defects. Venlafaxine had the highest proportion of elevated aORs with specific birth defects; escitalopram had the lowest proportion of elevated aORs (none).

Our findings on antidepressant use prevalence among US pregnant women[9,11,12] and factors associated with use[12,35,50,51] align with previous research. Associations between sertraline,[24,32,33,35,51] fluoxetine,[31,32,34,36,51] paroxetine,[30-36,51,52] and citalopram[31-34,36,51,52] and specific birth defects have been reported in multiple studies, including NBDPS[42]; research on escitalopram is limited. Reports using interim NBDPS data have been published on SSRIs,[38] venlafaxine,[41] bupropion,[40] and specific SSRIs (using bayesian methods to account for other published findings).[42] In this analysis, we used the final NBDPS data, adding 613 SSRI, 71 venlafaxine, and 187 bupropion-exposed women in early pregnancy to previous reports, which allowed us to examine previously reported associations for individual antidepressants and specific defects with more precision and explore additional birth defect associations.

Most previous studies[30-32,34,36,51,52] examining associations between individual antidepressants and specific birth defect risks have not accounted for the possible effects of the underlying condition. In our analysis, associations between the SSRIs and specific heart defects were largely attenuated when compared with women who took antidepressants only outside of early pregnancy. Our findings suggest that the elevated associations between heart defects and antidepressants may be confounded by the underlying condition; other work examining SSRI use and the risk of any heart defect has also concluded that associations between antidepressants and heart defects may be attributable to the underlying condition.[37,51] For each SSRI (except escitalopram), we noted some degree of higher risk for some nonheart defects among women taking antidepressants who were exposed during early pregnancy compared with those exposed outside of early pregnancy.

Among the non-SSRI antidepressants examined, venlafaxine had meaningfully elevated associations with many specific birth defects. Previous studies on venlafaxine have almost exclusively examined associations with any birth defect or any heart defect using teratogen information service[53,54] or administrative data.[32,55,56] These studies did not find an increased risk for combined birth defect groups after early pregnancy exposure.[22,32,53-56] An analysis of Nordic population data examined associations between venlafaxine and septal defects or hypospadias and concluded there was no association with either defect.[32] An earlier NBDPS analysis using data from 1997 to 2007 that did not account at least partially for the underlying condition[41] found that early pregnancy venlafaxine

Table 2. Characteristics of Control Mothers Exposed and Unexposed to Antidepressants Before and During Pregnancy in the National Birth Defects Prevention Study From 1997 to 2011

Characteristic[a]	No. (%)									
	Antidepressant use in mothers in the NBDPS			Among women with any antidepressant use during early pregnancy, characteristics by specific antidepressant[e]						
	No use before or during pregnancy (n = 10 886)[b]	Use solely outside of early pregnancy (n = 125)[c]	Any antidepressant use during early pregnancy (n = 467)[d]	Sertraline (n = 129)	Fluoxetine (n = 81)	Paroxetine (n = 43)	Citalopram (n = 39)	Escitalopram (n = 35)	Venlafaxine (n = 21)	Bupropion (n = 45)
Age, y										
<20	1094 (10.1)	10 (8.0)	22 (4.7)	8 (6.2)	4 (4.9)	1 (2.3)	2 (5.1)	0 (0)	1 (4.8)	0 (0)
20-24	2479 (22.8)	23 (18.4)	83 (17.8)	26 (20.2)	11 (13.6)	7 (16.3)	7 (18.0)	5 (14.3)	2 (9.5)	13 (28.9)
25-29	3009 (27.6)	35 (28.0)	132 (28.3)	31 (24.0)	27 (33.3)	17 (39.5)	8 (20.5)	7 (20.0)	7 (33.3)	13 (28.9)
30-34	2784 (25.6)	40 (32.0)	151 (32.3)	43 (33.3)	26 (32.1)	13 (30.2)	16 (41.0)	16 (45.7)	4 (19.1)	13 (28.9)
35-39	1267 (11.6)	16 (12.8)	66 (14.1)	18 (14.0)	10 (12.4)	4 (9.3)	5 (12.8)	6 (17.1)	7 (33.3)	5 (11.1)
≥40	253 (2.3)	1 (0.8)	13 (2.8)	3 (2.3)	3 (3.7)	1 (2.3)	1 (2.6)	1 (2.9)	0 (0)	1 (2.2)
Race/ethnicity[f]										
Non-Hispanic										
White	6178 (56.8)	97 (77.6)	396 (84.8)	107 (83.0)	67 (82.7)	35 (81.4)	34 (87.2)	32 (91.4)	17 (81.0)	42 (93.3)
Black	1224 (11.3)	6 (4.8)	19 (4.1)	7 (5.4)	3 (3.7)	2 (4.7)	2 (5.1)	0 (0)	1 (4.8)	0 (0.0)
Hispanic	2761 (25.4)	12 (9.6)	31 (6.6)	10 (7.8)	7 (8.6)	4 (9.3)	0 (0)	1 (2.9)	2 (9.5)	3 (6.7)
Other	717 (6.6)	10 (8.0)	21 (4.5)	5 (3.9)	4 (4.9)	2 (4.7)	3 (7.7)	2 (5.7)	1 (4.8)	0 (0.0)
Education, y										
<12	1818 (16.9)	21 (17.1)	43 (9.3)	13 (10.2)	9 (11.3)	7 (16.3)	3 (7.7)	0 (0)	1 (4.8)	2 (4.4)
12	2569 (23.9)	26 (21.1)	91 (19.7)	30 (23.6)	21 (26.3)	10 (23.3)	3 (7.7)	6 (17.1)	1 (4.8)	7 (15.6)
≥12	6376 (59.2)	76 (61.8)	328 (71.0)	84 (66.1)	50 (62.5)	26 (60.5)	33 (84.6)	29 (82.9)	19 (90.5)	36 (80.0)
Prepregnancy BMI										
<18.5	563 (5.4)	9 (7.3)	14 (3.0)	2 (1.6)	2 (2.5)	3 (7.0)	2 (5.1)	0 (0)	1 (4.8)	2 (4.6)
18.5-24.9	5606 (53.9)	60 (48.4)	251 (54.0)	73 (56.6)	48 (60.0)	25 (58.1)	19 (48.7)	15 (42.9)	8 (38.1)	27 (61.4)
25.0-29.9	2375 (22.8)	30 (24.2)	95 (20.4)	24 (18.6)	15 (18.8)	4 (9.3)	11 (28.2)	9 (25.7)	5 (23.8)	7 (15.9)
≥30.0	1866 (17.9)	25 (20.2)	105 (22.6)	30 (23.3)	15 (18.8)	11 (25.6)	7 (18.0)	11 (31.4)	7 (33.3)	8 (18.2)
Early pregnancy cigarette smoking[g]										
Yes	1866 (17.3)	37 (29.8)	133 (28.7)	37 (29.1)	19 (23.8)	17 (39.5)	11 (28.2)	9 (25.7)	4 (19.1)	16 (35.6)
No	8936 (82.7)	87 (70.2)	330 (71.3)	90 (70.9)	61 (76.3)	26 (60.5)	28 (71.8)	26 (74.3)	17 (80.9)	29 (64.4)
Early pregnancy alcohol use[g]										
Yes	3935 (36.5)	64 (51.6)	233 (50.4)	58 (45.7)	46 (57.5)	22 (51.2)	19 (48.7)	21 (61.8)	11 (52.4)	17 (37.8)
No	6833 (63.5)	60 (48.4)	229 (49.6)	69 (54.3)	34 (42.5)	21 (48.8)	20 (51.3)	13 (38.2)	10 (47.6)	28 (62.2)
Folic acid use[h]										
Yes	5712 (52.5)	72 (57.6)	281 (60.2)	77 (59.7)	49 (60.5)	18 (41.9)	26 (66.7)	26 (74.3)	11 (52.4)	28 (62.2)
No	5174 (47.5)	53 (42.4)	186 (39.8)	52 (40.3)	32 (39.5)	25 (58.1)	13 (33.3)	9 (25.7)	10 (47.6)	17 (37.8)
Pregnancy intention										
Wanted to be pregnant then	5298 (59.6)	51 (51.5)	200 (55.7)	64 (62.8)	39 (60.9)	14 (40.0)	17 (58.6)	11 (42.3)	8 (53.3)	17 (51.5)
Wanted to wait until later	1806 (20.3)	25 (25.3)	76 (21.2)	18 (17.7)	14 (21.9)	12 (34.3)	8 (27.6)	7 (26.9)	2 (13.3)	5 (15.2)
Did not want to be pregnant at all	1011 (11.4)	12 (12.1)	41 (11.4)	10 (9.8)	6 (9.4)	5 (14.3)	1 (3.5)	2 (7.7)	3 (20.0)	6 (18.2)
Did not care	777 (8.7)	11 (11.1)	42 (11.7)	10 (9.8)	5 (7.8)	4 (11.4)	3 (10.3)	6 (23.1)	2 (13.3)	5 (15.2)
Previous live births										
≥1	6525 (60.0)	85 (68.0)	309 (66.2)	84 (65.1)	51 (63.0)	32 (74.4)	28 (71.8)	22 (62.9)	13 (61.9)	34 (75.6)
None	4357 (40.0)	40 (32.0)	158 (33.8)	45 (34.9)	30 (37.0)	11 (25.6)	11 (28.2)	13 (37.1)	8 (38.1)	11 (24.4)
Plurality										
Multiple	265 (2.4)	3 (2.4)	10 (2.1)	3 (2.3)	0 (0)	0 (0)	0 (0)	1 (2.9)	2 (9.5)	2 (4.4)
Singleton	10 617 (97.6)	122 (97.6)	457 (97.9)	126 (97.7)	81 (100)	43 (100)	39 (100)	34 (97.1)	19 (90.5)	43 (95.6)

(continued)

Table 2. Characteristics of Control Mothers Exposed and Unexposed to Antidepressants Before and During Pregnancy in the National Birth Defects Prevention Study From 1997 to 2011 (continued)

Characteristic[a]	No. (%)									
	Antidepressant use in mothers in the NBDPS			Among women with any antidepressant use during early pregnancy, characteristics by specific antidepressant[e]						
	No use before or during pregnancy (n = 10 886)[b]	Use solely outside of early pregnancy (n = 125)[c]	Any antidepressant use during early pregnancy (n = 467)[d]	Sertraline (n = 129)	Fluoxetine (n = 81)	Paroxetine (n = 43)	Citalopram (n = 39)	Escitalopram (n = 35)	Venlafaxine (n = 21)	Bupropion (n = 45)
Study site[i]										
Arkansas	1348 (12.4)	24 (19.2)	66 (14.1)	20 (15.5)	9 (11.1)	3 (7.0)	4 (10.3)	6 (17.1)	3 (14.3)	7 (15.6)
California	1196 (11.0)	4 (3.2)	32 (6.9)	8 (6.2)	8 (9.9)	3 (7.0)	1 (2.6)	2 (5.7)	1 (4.8)	3 (6.7)
Georgia	1181 (10.9)	12 (9.6)	35 (7.5)	10 (7.8)	10 (12.4)	1 (2.3)	4 (10.3)	3 (8.6)	1 (4.8)	1 (2.2)
Iowa	1181 (10.9)	19 (15.2)	73 (15.6)	19 (14.7)	10 (12.4)	9 (20.9)	5 (12.8)	8 (22.9)	2 (9.5)	8 (17.8)
Massachusetts	1288 (11.8)	20 (16.0)	69 (14.8)	16 (12.4)	14 (17.3)	6 (14.0)	8 (20.5)	3 (8.6)	4 (19.1)	5 (11.1)
New Jersey	563 (5.2)	0 (0.0)	9 (1.9)	3 (2.3)	1 (1.2)	3 (7.0)	0 (0)	0 (0)	0 (0)	0 (0)
New York	914 (8.4)	8 (6.4)	35 (7.5)	11 (8.5)	5 (6.2)	5 (11.6)	2 (5.1)	1 (2.9)	1 (4.8)	4 (8.9)
North Carolina	903 (8.3)	14 (11.2)	47 (10.1)	11 (8.5)	6 (7.4)	5 (11.6)	3 (7.7)	6 (17.1)	4 (19.1)	6 (13.3)
Texas	1300 (11.9)	11 (8.8)	25 (5.4)	11 (8.5)	3 (3.7)	3 (7.0)	1 (2.6)	1 (2.9)	0 (0)	3 (6.7)
Utah	1012 (9.3)	13 (10.4)	76 (16.3)	20 (15.5)	15 (18.5)	5 (11.6)	11 (28.2)	5 (14.3)	5 (23.8)	8 (17.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NBDPS, National Birth Defects Prevention Study.

[a] Women with missing data on maternal characteristics were excluded from the analysis. There were less than 5% missing data for all maternal characteristics, with the exception of pregnancy intention (18.4%).

[b] No antidepressant use in the 3 months before conception through the end of pregnancy.

[c] Antidepressant use 2 or 3 months before conception or during the fourth to ninth months of pregnancy but no antidepressant use in early pregnancy (1 month before conception through the third month of pregnancy). This may include monotherapy or polytherapy antidepressant use within this period.

[d] Any antidepressant use regardless of individual medication or medication class in early pregnancy (1 month before conception through the third month of pregnancy), including less common medications. This may include monotherapy or polytherapy antidepressant use within this period. χ^2 Tests were run for each characteristic to compare (1) any antidepressant use in early pregnancy vs no antidepressant use in the 3 months before conception to the end of pregnancy and (2) any antidepressant use in early pregnancy vs any antidepressant use only outside of early pregnancy. For set 1, the findings from the χ^2 test rejected the null of no difference between groups for age, race/ethnicity, education, prepregnancy BMI, early pregnancy smoking and alcohol use, folic acid use, previous live births, and study site. For set 2, the findings from the χ^2 tests rejected the null of no difference between groups for education.

[e] Specific antidepressant monotherapy medication use in the month before conception through the third month of pregnancy when there was 0.2% or greater prevalence among control mothers.

[f] During the interview, mothers were asked to self-report their own racial/ethnic status as there may be racial/ethnic differences in risk factors for specific birth defects. Racial/ethnic groups were further collapsed during analysis because of small sample sizes for some racial/ethnic groups.

[g] In the month before conception through the third month of pregnancy.

[h] In the month before conception through the first month of pregnancy.

[i] Statewide data collection occurred in Arkansas, Iowa, New Jersey, and Utah; other sites included selected geographic regions within the state. Included years in each state were: Arkansas (1998-2011), California (1997-2011), Georgia (1997-2011), Iowa (1997-2011), Massachusetts (1997-2011), New Jersey (1998-2003), New York (1997-2002 and 2004-2011), North Carolina (2003-2011), Texas (1997-2007 and 2008-2011), and Utah (2003-2011).

use was associated with many birth defects. Our analyses of the earlier and later (1997-2007[41] and 2008-2011, respectively) NBDPS data indicated results were similar across the 2 samples. After accounting at least partially for the underlying condition, bupropion was only associated with diaphragmatic hernia. While several studies have suggested bupropion exposure does not result in increased risk for all birth defects combined,[57,58] other research has suggested early pregnancy bupropion use is associated with specific heart defects.[21,59]

Strengths and Limitations

The NBDPS is among the largest studies worldwide that examines risk factors for specific birth defects with systematic case verification, which allowed us to examine associations with specific defects more accurately than is possible with administrative data.[60,61] We examined self-reported monotherapy use of specific antidepressants across several antidepressant classes and associations with a range of birth defects while accounting for many possible confounders. We accounted at least partially for confounding by the underlying condition, which, to our knowledge, previous analyses have not commonly done. This has clinical relevance because findings from such analyses can support work to identify medications with the highest and lowest birth defect risks independent of the underlying condition. However, the NBDPS interview did not systematically ascertain diagnoses associated with drug treatment, limiting our ability to account directly for mental health conditions in our analyses.[12] Antidepressant selection is not random and is based on shared clinician-patient decision-making about safety and effectiveness; we were unable to examine how differential medication selection may have affected our results. There may also be differences in disease severity, relapse risk, or other clinical differences among women who select specific antidepressants, continue using antidepressants during pregnancy compared

with those who discontinue treatment before pregnancy, or those who initiate treatment after the first trimester. This may have resulted in bias in our comparison group of women exposed only outside of early pregnancy, which we were unable to account for in our analysis. Further, we did not account for the differential half-life of antidepressants,[62] which could have resulted in exposure during periods classified as unexposed. Recall bias because of the retrospective data collection and differing time to maternal interview between case and control mothers could have affected these results, potentially leading to differential misclassification of exposure and confounders. Because status as a case and control mother affected participation, results could also be affected by selection bias if antidepressant exposure was also associated with interview participation. As this analysis was hypothesis generating and not determining causality, we did not adjust for multiple testing in considering whether a medication and birth defect association met the criteria for an elevated association; each medication and birth defect association should be confirmed in other samples.

Conclusions

Depressive and anxiety disorder treatment during pregnancy remains clinically challenging, in part because of the competing reproductive safety risks of poorly treated mental health disorders and potential safety concerns regarding antidepressant treatment during pregnancy.[63,64] Many studies on the fetal safety of antidepressants have grouped medications into broad classes[65] that limit clinical usefulness. Our analysis, which focused on commonly prescribed individual antidepressants and specific birth defects, does not have this limitation. Our findings suggest varied risks for specific birth defects after early pregnancy use of individual SSRIs, venlafaxine, and bupropion, all of which are first-line antidepressants.[66] Our results indicated venlafaxine had the highest proportion of elevated birth defect risks while escitalopram had the fewest. However, to our knowledge, ours is among the few studies to examine associations between individual antidepressants and specific birth defects while at least partially accounting for the underlying condition and its corollaries, and our results need replication. Our findings underscore the importance of research on the relative reproductive and fetal safety of all first-line antidepressants. For women who require antidepressants during pregnancy, relative differences in the safety of specific medications may be useful to consider in risk-benefit decision-making. Fully informed decision-making requires balancing the risks and benefits of any proposed intervention against the maternal and fetal risks of untreated depression or anxiety, mindful that with every pregnancy an underlying risk of a birth defect exists regardless of antidepressant treatment.[67]

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Anderson, Mitchell, Riehle-Colarusso, Polen, Reefhuis.
Critical revision of the manuscript for important intellectual content: All authors.
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Other - Development of study design: Mitchell.

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