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The Association Between Reported Venlafaxine Use in Early Pregnancy and Birth Defects, National Birth Defects Prevention Study, 1997–2007

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Abstract

Background—Few epidemiologic studies have investigated the use of venlafaxine (Effexor®), an antidepressant used to treat major depression and anxiety disorders in adults, during pregnancy. Our objective was to determine whether use of venlafaxine during pregnancy is associated with specific birth defects.

Methods—We used data from the National Birth Defects Prevention Study (NBDPS), a population-based, case-control study in the United States. Our analysis included mothers with pregnancies affected by one of 30 selected birth defects (cases) and babies without birth defects (controls) with estimated dates of delivery between 1997–2007. Exposure was any reported use of venlafaxine from one month preconception through the third month of pregnancy. We calculated adjusted odds ratios (aORs) and 95% Fisher's Exact confidence intervals (CIs) for 24 birth defect groups for which at least 400 case mothers were interviewed. Our adjusted analyses controlled for maternal age and race-ethnicity.

Results—Among the 27,045 NBDPS participants who met inclusion criteria, 0.17% (14/8,002) of control mothers and 0.40% (77/19,043) of case mothers reported any use of venlafaxine from one month preconception through the third month of pregnancy. Statistically significant associations were found for anencephaly, atrial septal defect (ASD) secundum or ASD not otherwise specified, coarctation of the aorta, cleft palate, and gastroschisis.

Conclusions—Our data suggest associations between periconceptional use of venlafaxine and some birth defects. However, sample sizes were small, confidence intervals were wide, and additional studies are needed to confirm these results.

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Keywords

Venlafaxine; Birth Defects; Pregnancy; Antidepressants; Epidemiology

Introduction

Venlafaxine (Effexor®) is a medication that is used to treat major depressive, generalized anxiety and social anxiety disorders in adults. The prevalence of depression during pregnancy is about 18% and the prevalence of generalized anxiety disorders is estimated to be 8.5% among pregnant women (Ross and McLean, 2006; Yonkers and others, 2009). Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI), which functions to block the reuptake of both serotonin and norepinephrine, and at high doses, also may affect reuptake of dopamine (Sussman, 2003). The mechanism of action for SNRIs is similar to another common class of antidepressants, selective-serotonin reuptake inhibitors (SSRIs), which act to block the reuptake of serotonin alone (Sussman, 2003).

Few epidemiologic studies have investigated the use of venlafaxine during pregnancy and birth defects. Because of small numbers, some studies have grouped exposure to venlafaxine with exposure to SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) or other newer antidepressants, which does not allow for examination of specific effects of venlafaxine exposure separate from these other antidepressant medications (Einarson and others, 2009; Ferreira and others, 2007; Kallen, 2004b; Lennestall and Kallen, 2007; Reis and Kallen, 2010; Wichman and others, 2009; Yaris and others, 2004). In general, these studies found no associations between major malformations and SNRI medications as a group. Of those who assessed venlafaxine separately, no significant associations were observed. For example, a study by Einarson and colleagues found no significant differences in the prevalence of birth defects between women who were exposed to venlafaxine and women exposed to SSRIs or medications believed to be non-teratogenic during pregnancy (n=150 per group) (Einarson and others, 2001; Oberlander and others, 2008). Similarly, Oberlander and colleagues used administrative health data to look at serotonin reuptake inhibitors including venlafaxine, individually and as a group, and found no increased risk for birth defects overall or specifically for cardiac defects when compared to women unexposed to SSRIs, SNRIs, and benzodiazepines (Oberlander and others, 2008).

Several studies have examined the associations between use of SSRIs during pregnancy and birth defects and have reported mixed results. Some suggest that SSRIs might be associated with an increased risk of heart defects, mainly septal defects and right ventricular outflow tract obstruction (RVOTO) defects (Bar-Oz and others, 2007; Berard and others, 2007; Cole and others, 2007; Diav-Citrin and others, 2008; Einarson and others, 2008; Ferreira and others, 2007; Kallen, 2004a; Kallen and Otterblad Olausson, 2007; Louik and others, 2007). A previous analysis of data from the National Birth Defects Prevention Study (NBDPS) showed associations between SSRIs and anencephaly, craniosynostosis, and omphalocele (Alwan and others, 2007). A similar study by Louik and colleagues found associations between individual SSRIs and certain birth defects, such as sertraline and septal heart defects, sertraline and omphalocele, and paroxetine and right ventricular outflow tract

obstruction defects (Louik and others, 2007). Although SSRIs and SNRIs might function similarly to treat depressive symptoms, much less is known about the risk of SNRIs (such as venlafaxine) and their use during pregnancy.

We used data from the NBDPS to assess whether reported use of venlafaxine just before and during early pregnancy is associated with specific birth defects.

Methods

Study Population

The NBDPS is an ongoing, population-based, case-control study designed to investigate genetic and environmental risk factors for major structural birth defects (Rasmussen and others, 2003; Yoon and others, 2001). Birth defects data are collected by ten birth defects surveillance systems in the United States: Arkansas (statewide), California (region near Fresno), Georgia (metropolitan Atlanta), Iowa (statewide), Massachusetts (eastern counties), New Jersey (statewide, ending in 2002), New York (western NY and Hudson Valley), North Carolina (19 central counties, beginning in 2003), Texas (varying regions, currently Health Service Region 11), and Utah (statewide, beginning in 2003). The study was approved by institutional review boards of the Centers for Disease Control and Prevention and all study centers.

Cases include live births, stillbirths (< 20 weeks gestation), and elective terminations diagnosed with one of more than 30 selected major birth defects. To focus on birth defects of unknown etiology, infants with recognized or strongly suspected chromosomal abnormalities or single-gene disorders are excluded. Control infants are liveborn infants without birth defects randomly selected from hospital birth records or birth certificate records from the same source population and time period as the case infants. To confirm study eligibility, all case records are reviewed by clinical geneticists to determine if they meet the standard case definitions. Clinical information on infants with heart defects also are reviewed by clinicians with expertise in pediatric cardiology. All heart defect diagnoses are confirmed using reports from echocardiography, cardiac catheterization, surgery, or autopsy (Yoon and others, 2001).

Mothers of case and control infants are contacted within 6 weeks to 24 months after the estimated date of delivery (EDD). If the mother agrees to participate in the study, a trained interviewer administers a standardized computer-assisted telephone interview in English or Spanish. The interview ascertains specific exposures and behaviors throughout pregnancy and the three months preconception. During the interview, mothers are asked about maternal and paternal demographic characteristics, pregnancy history, medication and vitamin use, dietary details, drug and alcohol use, occupational exposures, and reproductive health information.

Venlafaxine Exposure

Exposure was defined as any reported use of venlafaxine from one month before conception through the third month of pregnancy (periconceptional). This exposure definition does include timing outside of organogenesis; however, because it is possible that women may

not recall dates exactly correctly (of pregnancy or of timing of the medication use), we included a broader time frame. During the medication portion of the NBDPS interview, mothers are asked about prescription and non-prescription medications that they may have taken from 3 months before conception through delivery. Interviewers read a list of brand name medications (e.g., Prozac®, Zoloft®) to the mothers, and after each medication is read, mothers respond yes or no to report if they had taken the medication. At the end of the list, they are asked if they had taken any medications that were not mentioned. For births with an EDD during 1997–2005, venlafaxine (Effexor®) was not one of the specific medications listed. In 2005, the interview was revised, and Effexor® (the more commonly recognized brand name for venlafaxine) was added to the list of medications that were read. Thus, for births with an EDD during 2006–2007, mothers responded yes or no when they heard venlafaxine listed. In addition, during the maternal health portion of the NBDPS interview, mothers are asked open-ended questions about illnesses or diseases they may have had during pregnancy and about any medications used for this illness. Regardless of where in the interview the mother reported use of a specific medication, subsequent questions were asked regarding start date, stop date, and frequency of use. If a mother reported any brand (Effexor®) or generic (venlafaxine) name for venlafaxine and reported periconceptional use of the antidepressant, they were classified as exposed.

Statistical Analysis

These analyses were limited to mothers who had an EDD after October 1, 1997 through December 31, 2007. We excluded mothers who did not complete the maternal interview through all of the medication questions and included only those birth defect groups for which there were at least 400 case mothers interviewed. Due to the strong association observed between pre-pregnancy diabetes and birth defects, we excluded mothers who reported pre-pregnancy type 1 or type 2 diabetes (Correa and others, 2008). To assess effects of venlafaxine separate from other antidepressants, mothers who reported other periconceptional antidepressant use were excluded. Lastly, we excluded mothers who had missing information on the timing of exposure during pregnancy or who were exposed to venlafaxine outside the periconceptional window of interest (Figure 1). Women were classified as unexposed if they did not report use of any antidepressant from three months before conception through the end of pregnancy.

To examine the association between exposure to venlafaxine and the occurrence of birth defects, we estimated crude and adjusted odds ratios (ORs) and 95% Fisher's Exact confidence intervals (CIs) if there were more than 2 exposed cases. Because of the small number of exposed mothers, we controlled for only two variables chosen *a priori*: maternal age (<30, 30 years) and race/ethnicity (non-Hispanic white, other). Because gastroschisis is associated with young maternal age, the association with gastroschisis was adjusted for maternal age (<20, 20 years) and race/ethnicity (non-Hispanic white, other). These factors were self-reported during the maternal interview. Birth defect groups are not mutually exclusive; case infants with more than one birth defect are included in more than one category. Therefore, we conducted a sub-analysis restricted to cases with isolated birth defects, estimating crude ORs (cORs) because of decreased sample size.

After reviewing preliminary results, post-hoc analyses were performed to further understand observed associations. Fewer case and control mothers with EDDs from 1997–2002 reported using venlafaxine. Therefore, we conducted sub-analyses limiting the data to the most recent 5-year time period (EDD: 2003–2007), estimating cORs and 95% Fisher's Exact CIs. We also examined other medications reported and other illnesses or diseases reported by venlafaxine-exposed mothers. To explore the role of recall bias, we estimated cORs under the assumption that, among controls only, 30% of exposed mothers erroneously had not reported exposure. In this hypothetical scenario, we assumed that 20 control mothers were truly exposed; therefore, in addition to the 14 control mothers who reported exposure, six more mothers were actually exposed but failed to report it (6/20=30%). We calculated hypothetical cORs under these assumptions to assess the effect of potential under-reporting among control mothers.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC).

Results

Among mothers who met our inclusion criteria, 0.17% (14/8,002) of control mothers and 0.40% (77/19,043) of case mothers reported any periconceptional use of venlafaxine. Duration of use ranged from 1–120 days, but the majority (54%) of mothers reported using venlafaxine for the entire period of one month before pregnancy through the end of the first trimester. Exposure was more likely among those with a higher education and of non-Hispanic white race-ethnicity. These mothers also more frequently reported any folic acid use from one month preconception through the first month of pregnancy (Table 1). Of the exposed mothers, only 24% had EDDs during 1997–2002; the remaining 76% of exposed mothers had EDDs from 2003–2007 (Table 1).

We assessed 24 groups of birth defects that had 400 or more case infants. One group, esophageal atresia (n=499), had no mothers exposed to venlafaxine, and six groups had 2 or fewer mothers exposed: anotia/microtia, d-transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart syndrome, anorectal atresia, and diaphragmatic hernia. ORs were not assessed for these seven defects (Table 2). We observed all effect estimates to be elevated, but select groups had statistically significantly elevated ORs: anencephaly; septal heart defects, likely driven by the association with the subcategory atrial septal defect secundum (ASD) or ASD not otherwise specified; left ventricular outflow tract obstruction (LVOTO) defects, likely driven by the association with the subcategory coarctation of the aorta; cleft palate; and gastroschisis (Table 2).

When restricting analysis to isolated birth defects, the majority of associations remained statistically significant, although differences were observed for some groups. Effect estimates for some associations, including anencephaly, cleft palate alone, and gastroschisis, increased slightly (cOR: 6.2; 95% CI: 1.5–20.0; cOR: 4.4; 95% CI: 1.5–11.6; and cOR: 4.2; 95% CI: 1.3–11.7, respectively). The association with LVOTO defects decreased (cOR: 3.1; 95% CI: 1.1–8.3), likely because the association with subcategory coarctation of the aorta was no longer statistically significant (cOR: 3.5; 95% CI: 0.8–11.1).

In our post-hoc analyses restricting the data to EDDs in the most recent 5-year time period, effect estimates remained elevated; however, most were no longer statistically significant. The associations with anencephaly and LVOTO defects remained statistically significantly elevated, while the associations with cleft palate and gastroschisis were of borderline significance (Table 3).

In our post-hoc evaluation of other medications or illnesses during pregnancy, we did not observe any patterns among venlafaxine-exposed mothers. Two exposed case mothers (2.6%) were also exposed to high blood pressure medications, seven exposed case mothers (9.0%) were exposed to antiepileptic medications (not valproic acid), and two exposed case mothers (2.6%) reported opioid analgesic medications. Among these mothers exposed to multiple medications, no patterns of medications or of birth defects were observed. For example, three of the case mothers exposed to venlafaxine were also exposed to clonazepam, an antiepileptic medication, but each of their infants had a different condition: cleft palate, an association of heart defects—ASD and ventricular septal defect, and tetralogy of Fallot. In the open-ended questions about general illness during pregnancy, responses varied; however, no pattern of other illness was observed among venlafaxine-exposed mothers (data not shown).

In our post-hoc analysis exploring recall bias, we re-assessed the crude associations assuming under-reporting among control mothers. If we assumed 30% of exposed control mothers did not report exposure, all associations remained elevated, although closer to the null. For example, the association with anencephaly decreased to 3.9 (95% CI: 1.1–11.8). In this hypothetical scenario, the association with coarctation of the aorta decreased to 3.1 (95% CI: 1.0–8.1), and the association with cleft palate alone decreased to 2.5 (95% CI: 0.9–6.1).

Discussion

Using data from the NBDPS, a multi-site, population-based case-control study in the United States, we observed that periconceptional venlafaxine exposure might be associated with certain birth defects, specifically anencephaly, cleft palate, gastroschisis, and some heart defects, such as ASD secundum or ASD not otherwise specified and coarctation of the aorta. However, because these analyses were based on a small number of exposed cases, many of the estimates were imprecise with wide confidence intervals.

Reported exposure to venlafaxine during early pregnancy increased among all mothers over time. This corroborates previous studies that have shown an increase in antidepressant use in the United States over time (Harman and others, 2009; Marcus and Olfson, 2010; Olfson and Marcus, 2009), including use among pregnant women (Alwan and others, 2011; Andrade and others, 2008; Cooper and others, 2007).

Our findings differed from earlier studies. One prospective cohort study by Einarson and colleagues enrolled pregnant women via seven pregnancy counseling centers. The authors compared venlafaxine-exposed women to women exposed to SSRIs and women exposed to medications believed to be non-teratogenic during pregnancy. Two of the exposed babies

had a major malformation; however, no significant differences were found between the three groups. This study consisted of a small number of subjects, which limited its ability to examine associations with rare outcomes (Einarson et al., 2001). Oberlander and colleagues used linked administrative health data and prescription information to determine venlafaxine exposure during the first trimester. They found no increased risk of birth defects overall or for cardiovascular defects compared to women unexposed to SSRIs, other SNRIs, and benzodiazepines (Oberlander et al., 2008). Of the limited information from animal studies, one study reported that venlafaxine use during pregnancy had adverse effects on rat fetuses (da-Silva and others, 1999), but studies on rats and rabbits performed by the manufacturer found no teratogenic effects (2007).

Biologically, venlafaxine functions in the nervous system by blocking the reuptake of two neurotransmitters, serotonin and norepinephrine, at the synaptic junction (2007). During embryogenesis, these neurotransmitters are expressed in early phases, potentially playing a role as early as gastrulation (Lauder, 1988). It is believed that these neurotransmitters may act as morphogens, signaling molecules that have a dose-dependent function on receptive cells (Buznikov and others, 2001; Lauder, 1988). Several animal studies have provided specific evidence for serotonin acting as a morphogen in craniofacial and cardiac development (Choi and others, 1997; Cote and others, 2007; Moiseiwitsch, 2000; Moiseiwitsch and Lauder, 1995; Nebigil and others, 2000; Nebigil and Maroteaux, 2001). Studies have also shown that norepinephrine influences neural crest cell formation and differentiation during embryogenesis (Hu and others, 2009; Ren and others, 2001; Ren and others, 2003; Sieber-Blum and Ren, 2000; Zhang and others, 1997). Thus, if venlafaxine is taken during early pregnancy and interferes with these embryologic signaling pathways, it is plausible that venlafaxine could affect craniofacial and cardiac development. This is consistent with our findings of associations with septal heart defects, LVOTO defects and cleft palate.

Another potential explanation for the associations observed is that women who use venlafaxine have underlying differences compared to non-users. Some differences in demographic and lifestyle factors between exposed and unexposed mothers were noted. For example, exposure was more common among non-Hispanic white mothers and folic acid users. However, no differences were observed between venlafaxine-exposed and unexposed mothers in terms of potential risk factors such as exposure to cigarette smoking or alcohol consumption during early pregnancy. We also looked at exposure to other medications that might increase the risk for birth defects; however, no patterns were observed.

Because venlafaxine is a second-line treatment that is prescribed to individuals that do not respond well to first-line treatments like SSRIs (Schueler and others, 2011), it is possible that women treated with venlafaxine have more severe disease or underlying differences in their depression, which might account for the associations we observed. Depression, itself, has been shown to be associated with a number of adverse pregnancy outcomes, such as spontaneous abortion, fetal death, low birth weight, and preterm birth (Bonari and others, 2004; Grote and others, 2010). In our study, over 50% of venlafaxine-exposed mothers reported using the medication during the entire early pregnancy period, which suggests long-term treatment. Although we ask questions in the maternal interview about maternal disease,

we do not have specific questions about depression, so we are unable to assess confounding by indication.

Given that the maternal interview took place after the birth outcome is known and that we found all effect estimates to be elevated, we were concerned about recall bias. In our post-hoc analysis examining the potential role of under-reporting among control mothers, effect estimates remained elevated, although were closer to the null, suggesting that our observed results were unlikely the result of significant recall bias. Our assumption that 30% of exposed control mothers did not report exposure is likely too high; the magnitude of under-reporting is probably smaller. Previous studies have shown that recall bias might not have as considerable an effect in practice as one might expect (Drews and others, 1990; Khoury and others, 1994; Mackenzie and Lippman, 1989; Zierler and Rothman, 1985). In the NBDPS, we study a number of different medications, including antidepressant exposures, and previous NBDPS studies have not observed a broad increase in the number of elevated associations with birth defects. Thus, it is not likely that recall bias would play a major role for venlafaxine, but not other NBDPS exposures (Alwan and others, 2010; Alwan and others, 2007). Additionally, it has been shown that asking about medications in relation to treating illness as well as asking directly about specific medications can improve postnatal recall (Mitchell and others, 1986). Both techniques are utilized in the NBDPS interview, but venlafaxine was not included in the list of specific medications listed until 2006; however, first line medications for depression (e.g., paroxetine, fluoxetine, sertraline) have always been included, probably prodding the report of other antidepressants as well. Differential reporting of exposure between case and control mothers might occur because of differences in the timing of the interview after birth. However, average time to interview is relatively similar for both case and control mothers—about 11 months for case mothers and about 9 months for control mothers.

Our analysis should be interpreted in light of several additional limitations. In the maternal interview, mothers are asked about the frequency of medication use but not the dose, which could affect dose-response relationships. Since the mothers are asked to recall pregnancy exposures and the information collected during the interview was not validated, misclassification of exposures is possible. Since venlafaxine was not specifically asked about in the maternal interview until 2006, it is possible the medication was under-reported during the earlier time period. Because we conducted a large number of tests, some of the associations may be due to chance. We examined associations with 24 groups of birth defects at the 0.05 significance level, so we would expect at least 1 positive result to occur by chance. It is possible that by selecting groups of birth defects with at least 400 cases, we inadvertently selected for those with elevated risk point estimates. Another potential limitation to consider is that NBDPS study centers may have under-ascertained cases that were prenatally diagnosed and terminated. This would most likely affect birth defects with higher proportions of terminations (e.g., anencephaly, spina bifida, or omphalocele), and this potential under-ascertainment might have biased the results for these birth defect outcomes (Waller and others, 2000). Lastly, the NBDPS had a non-participation rate of about 30%; however, it is unlikely that participation would differ between cases and controls based on whether or not the woman used venlafaxine. A previous analysis that investigated selection bias in the NBDPS determined that, although there were some small statistically significant

differences in some demographic characteristics, the NBDPS control population is generally representative of the base population (Cogswell and others, 2009).

Strengths of our study include the fact that our data come from a large, population-based, case-control study, which allowed us to look at a large number of birth defect groups and the ability to examine venlafaxine exposure separate from other antidepressant medications. All the defects included have consistent case definitions, and the cases in the study are classified by clinical experts in genetics and pediatric cardiology.

In conclusion, our data suggest that maternal periconceptional use of venlafaxine might be associated with certain birth defects, specifically anencephaly, cleft palate, gastroschisis, and some heart defects, such as ASD secundum or ASD not otherwise specified and coarctation of the aorta. However, our analyses are based on a small number of mothers exposed to venlafaxine during early pregnancy, which led to imprecise estimates with wide confidence intervals. Additional studies are needed to confirm these results.

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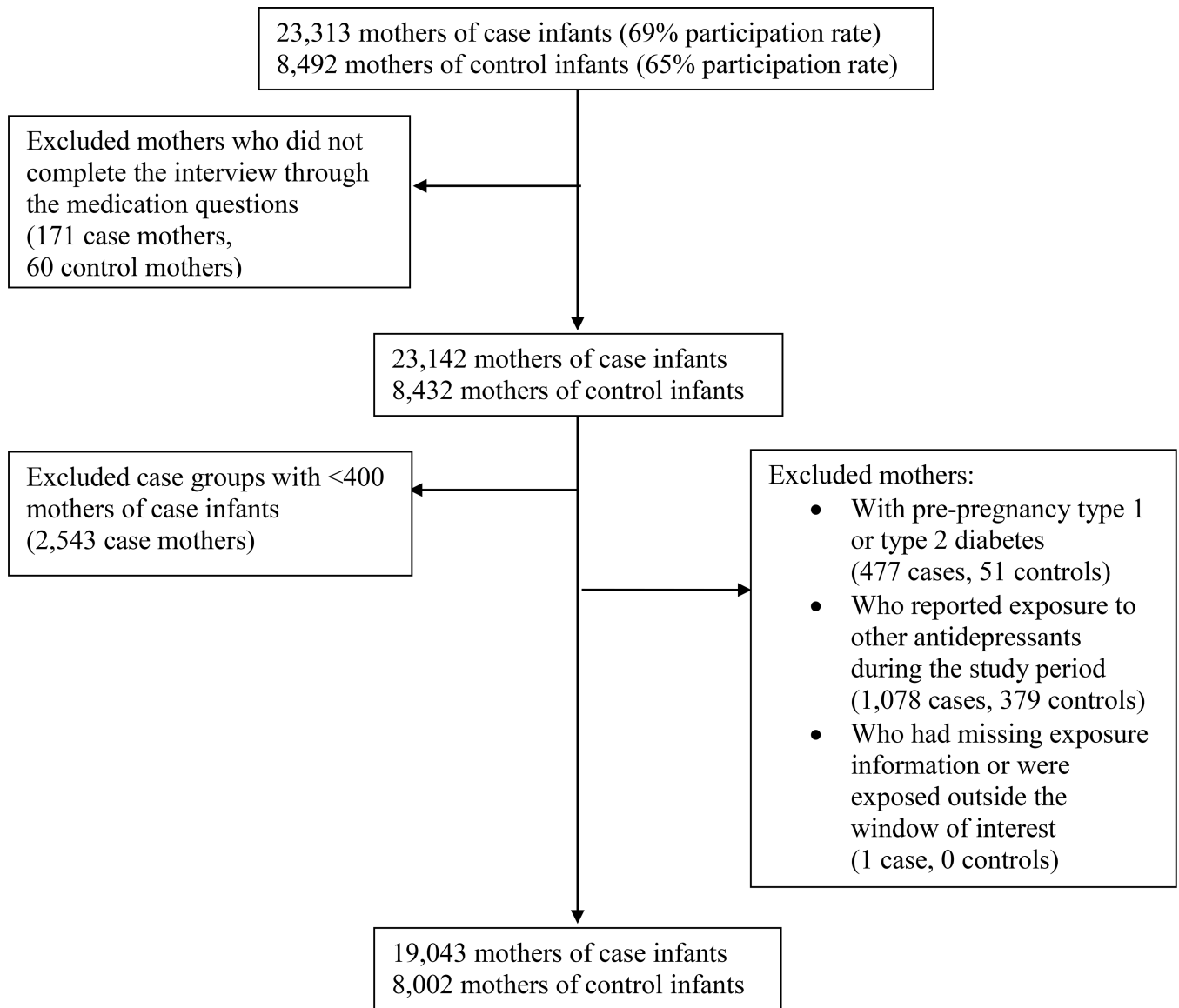


Figure 1. Flow diagram showing study participation rates and exclusion criteria for mothers of case and control infants in the analyses of venlafaxine and birth defects, National Birth Defects Prevention Study, 1997–2007

Demographic and Lifestyle Characteristics of Mothers, Exposed and Unexposed to Venlafaxine During Early Pregnancy, National Birth Defects Prevention Study, 1997–2007

Table 1

	Used Venlafaxine (n=91)		Unexposed (n=26,954)		P-value
	n	%	n	%	
Age					
<30 years	48	52.8	16344	60.6	0.12
30 years	43	47.2	10610	39.4	
Education					
High School	19	20.9	11594	43.0	<0.01
>High School	72	79.1	15107	56.0	
Missing			253	0.9	
Race					
NH White	83	91.2	15778	58.5	<0.01
Other	8	8.8	11167	41.4	
Missing			9	0.0	
Obesity¹					
Yes	23	25.3	4558	16.9	0.06
No	68	74.7	21171	78.5	
Missing			1225	4.5	
Smoking²					
Any	21	23.1	5150	19.1	0.35
None	70	76.9	21612	80.2	
Missing			192	0.7	

	Used Venlafaxine (n=91)		Unexposed (n=26,954)		P-value
	n	%	n	%	
Alcohol²					
Any	39	42.9	9678	35.9	0.19
None	52	57.1	16986	63.0	
Missing			290	1.1	
Folic Acid Use³					
Any	67	73.6	13477	50.0	<0.01
None	24	26.4	13477	50.0	
Parity					
No previous live birth	32	35.2	11338	42.1	0.18
At least 1 previous live birth	59	64.8	15585	57.8	
Missing			31	0.1	
Estimated Date of Delivery					
1997	0	0	308	1.1	<.01
1998	2	2.2	2359	8.8	
1999	1	1.1	2769	10.3	
2000	5	5.5	2946	10.9	
2001	3	3.3	2725	10.1	
2002	11	12.1	2385	8.9	
2003	6	6.6	2591	9.6	
2004	19	20.9	3020	11.2	
2005	17	18.7	2825	10.5	
2006	12	13.2	2509	9.3	
2007	15	16.5	2517	9.3	
Study Centers					

	Used Venlafaxine (n=91)		Unexposed (n=26,954)		P-value
	n	%	n	%	
Arkansas	16	17.6	3515	13.0	<.01
California	7	7.7	3505	13.0	
Georgia/CDC	7	7.7	3062	11.4	
Iowa	16	17.6	2601	9.7	
Massachusetts	9	9.9	3451	12.8	
New Jersey	1	1.1	1957	7.3	
New York	5	5.5	2048	7.6	
North Carolina	5	5.5	1561	5.8	
Texas	6	6.6	3232	12.0	
Utah	19	20.9	2022	7.5	

¹ Obesity is defined as a body mass index greater than or equal to 30 and is based on self-reported height and weight.

² 1 month prior to pregnancy through third month of pregnancy

³ 1 month prior to pregnancy through first month of pregnancy

Table 2

Association between use of venlafaxine just before and during early pregnancy and the occurrence of certain birth defects, National Birth Defects Prevention Study, 1997–2007

Birth Defects	Total	Exposed	Crude Odds Ratio 95% Exact CI	Adjusted Odds Ratio ¹ 95% Exact CI
No Major Birth Defects (Control Infants)	8002	14	1.0 (ref)	1.0 (ref)
Anencephaly	411	4	5.6 (1.3–18.0)	6.3 (1.5–20.2)
SpinaBifida	874	3	2.0 (0.4–7.1)	2.1 (0.4–7.6)
Anotia or Microtia	470	1	§	§
Conotruncal Heart Defects	1754	6	2.0 (0.6–5.4)	1.9 (0.6–5.3)
D-Transposition of the Great Arteries	545	2	§	§
Tetralogy of Fallot	799	1	§	§
Septal Heart Defects	3621	18	2.9 (1.3–6.2)	3.0 (1.4–6.4)
Perimembranous Ventricular Septal Defect	1410	6	2.4 (0.8–6.8)	2.4 (0.8–6.7)
Atrial Septal Defect, type 2 or not otherwise specified	2181	11	2.9 (1.2–6.9)	3.1 (1.3–7.4)
Ventricular Septal Defect-Atrial Septal Defect Association	576	3	3.0 (0.5–10.8)	3.1 (0.6–11.3)
Right Ventricular Outflow Tract Obstruction Defects ²	1250	5	2.3 (0.6–6.7)	2.3 (0.6–6.6)
Pulmonary Valve Stenosis	985	5	2.7 (0.8–8.1)	2.7 (0.8–7.9)
Left Ventricular Outflow Tract Obstruction Defects	1444	9	3.6 (1.4–8.9)	3.3 (1.2–8.2)
Hypoplastic Left Heart Syndrome	425	2	§	§
Coarctation of the Aorta	768	6	4.5 (1.4–12.5)	4.1 (1.3–11.5)
Cleft Lip with or without Cleft Palate	2134	6	1.6 (0.5–4.4)	1.5 (0.5–4.3)
Cleft Palate alone	1123	7	3.5 (1.2–9.3)	3.3 (1.1–8.8)
AnorectalAtresia	741	1	§	§
Esophageal Atresia	499	0	§	§
Hypospadias, 2 nd /3 rd degree ³	1571	7	2.6 (0.8–8.7)	2.3 (0.7–7.9)
Any Limb Reduction Defect	847	3	2.0 (0.4–7.3)	2.1 (0.4–7.6)
Craniosynostosis	982	3	1.7 (0.3–6.3)	1.5 (0.3–5.4)
Diaphragmatic Hernia	594	2	§	§
Gastroschisis	911	6	3.8 (1.2–10.5)	5.7 (1.8–15.9)⁴

§ Two or fewer exposed cases; No odds ratios calculated.

¹ Adjusted for age (<30, 30 years) and race (NH White, Other)

² Excluding Ebstein's Anomaly

³ Hypospadias among male infants only; 4063 control male infants

⁴ Association with gastroschisis adjusted for age (<20, 20 years) and race (NH White, Other)

Table 3

Association between use of venlafaxine just before and during early pregnancy and the occurrence of certain birth defects, National Birth Defects Prevention Study, Restricted to 2003–2007

Birth Defects	Total	Exposed	Crude Odds Ratio (Exact 95% CI)
No Major Birth Defects (Control Infants)	4038	12	1.0 (ref)
Anencephaly	210	4	6.5 (1.5–21.7)
SpinaBifida	431	2	§
Anotia or Microtia	216	1	§
Conotruncal Heart Defects	826	3	1.2 (0.2–4.5)
D-Transposition of the Great Arteries	254	2	§
Tetralogy of Fallot	388	0	§
Septal Heart Defects	1795	11	2.1 (0.8–5.1)
Perimembranous Ventricular Septal Defect	659	4	2.0 (0.5–6.8)
Atrial Septal Defect type 2 or not otherwise specified	1221	6	1.7 (0.5–4.8)
Ventricular Septal Defect-Atrial Septal Defect Association	308	1	§
Right Ventricular Outflow Tract Obstruction Defects ¹	669	3	1.5 (0.3–5.6)
Pulmonary Valve Stenosis	543	3	1.9 (0.3–6.9)
Left Ventricular Outflow Tract Obstruction Defects	790	7	3.0 (1.0–8.3)
Hypoplastic Left Heart Syndrome	220	2	§
Coarctation of the Aorta	427	4	3.2 (0.7–10.5)
Cleft Lip with or without Cleft Palate	1036	5	1.6 (0.4–4.8)
Cleft Palate alone	522	5	3.1 (0.9–9.6)
AnorectalAtresia	344	1	§
Esophageal Atresia	215	0	§
Hypospadias, 2 nd /3 rd degree ²	777	6	3.2 (0.8–13.5)
Any Limb Reduction Defect	385	3	2.6 (0.5–9.8)
Craniosynostosis	574	2	§
Diaphragmatic Hernia	305	1	§
Gastroschisis	508	5	3.3 (0.9–10.2)

§ Two or fewer exposed cases; No odds ratios calculated.

¹ Excluding Ebstein's Anomaly

² Hypospadias among male infants only; 2089 control male infants