OBSTETRICS

# Maternal use of bupropion and risk for congenital heart defects

Sura Alwan, MSc; Jennita Reefhuis, PhD; Lorenzo D. Botto, MD; Sonja A. Rasmussen, MD, MS; Adolfo Correa, MD, MPH; Jan M. Friedman, MD, PhD; and the National Birth Defects Prevention Study

**OBJECTIVE:** We sought to determine if maternal bupropion treatment in early pregnancy is associated with congenital heart defects in the infant.

**STUDY DESIGN:** We conducted a retrospective case-control study of birth defects risk factors. Data on 6853 infants with major heart defects were compared with 5869 control infants born in 1997–2004. Bupropion exposure was defined as any reported use between 1 month before and 3 months after conception.

**RESULTS:** Mothers of infants with left outflow tract heart defects were more likely to have reported taking bupropion than mothers of control infants (adjusted odds ratio, 2.6; 95% confidence interval, 1.2–5.7; $P = .01$).

**CONCLUSION:** We identified a positive association between early pregnancy bupropion use and left outflow tract heart defects; however, the magnitude of the observed increased risk was small. Nevertheless, further studies are needed to confirm these results.

**Key words:** birth defects, bupropion exposure, congenital heart defects, pregnancy

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Bupropion is an aminoketone that is structurally and chemically different from other antidepressants on the market. It is a weak inhibitor of neuronal uptake of dopamine, norepinephrine, and serotonin and does not inhibit monoamine oxidase.[1] Bupropion was first marketed as an oral antidepressant (Wellbutrin; GlaxoSmithKline, London, UK) and was subsequently developed as a nonnicotine aid to smoking cessation (Zyban; GlaxoSmithKline).[2] Major depression among women of reproductive age is common,[3] and women who smoke are encouraged to stop doing so when they become pregnant.[4] It is, therefore, not surprising that some women are treated with bupropion early in pregnancy.[5] Nevertheless, available data on the safety of such treatment in human pregnancy are limited.

The manufacturer, GlaxoSmithKline, established a Bupropion Pregnancy Registry in 1997 to follow up the outcomes of pregnancies in which women took this drug. By the end of March 2008, congenital anomalies had been reported in 24 of 675 (3.6%) infants of women identified prospectively to have taken bupropion in the first trimester and reported to the registry. These included 651 live births without birth defects, 18 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects. Congenital heart defects were observed in 9 (1.3%) of these infants.[6] The registry used voluntary recruitment and reporting, which may lead to incomplete or biased reporting of pregnancies or outcomes. Most outcome reports were from clinicians who cared for the mother during her pregnancy and who may only have had information on birth defects diagnosed within a short time after birth, and the registry did not collect data on a comparison group. The registry also received retrospective notification of bupropion-exposed pregnancies after their outcomes were known. Of 28 retrospectively reported birth defects with maternal bupropion exposure (including 25 involving first-trimester exposure), there were 12 reports of congenital heart defects.[6]

These findings raised concern about the possibility of an association between maternal bupropion use early in pregnancy and congenital heart defects in the infant,[7] which prompted the manufacturer to undertake a retrospective cohort study of claims records of a large managed care database. That study did not find an association with cardiovascular

From the Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada (Ms Alwan and Dr Friedman); the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA (Drs Reefhuis, Rasmussen, and Correa); and the Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT (Dr Botto).

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Reprints: Jennita Reefhuis, PhD, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Rd., MS E-86, Atlanta, GA 30333. JReefhuis@cdc.gov.

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defects among infants of women who had received prescriptions for bupropion during the first trimester of pregnancy when compared with infants whose mothers had received prescriptions for other antidepressants during pregnancy or infants whose mothers received bupropion prescriptions outside the first trimester.[8]

We used data from the National Birth Defects Prevention Study (NBDPS), a population-based case-control study, to determine if maternal bupropion exposure in early pregnancy is associated with ≥1 selected category of congenital heart defects in the infant. We also carried out an exploratory analysis to compare the prevalence of maternal bupropion use among the mothers of infants with 6 categories of noncardiac defects.

## Materials and Methods

The NBDPS is an ongoing, multisite case-control study of environmental and genetic risk factors for >30 selected categories of major birth defects. Case infants were ascertained by population-based birth defects surveillance systems at 10 study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah).[9] We used data on infants born on or after Oct. 1, 1997, who had an estimated date of delivery on or before Dec. 31, 2004. Case infants were either live births (all participating sites), fetal deaths >20 weeks' gestation (Arkansas, California, Georgia, Iowa, Massachusetts, New York [since 2000], North Carolina, Texas, and Utah), or electively terminated pregnancies with reliably ascertained defects (Arkansas, California, Georgia, Iowa, New York [since 2000], North Carolina, Texas, and Utah). Infants with recognized or strongly suspected chromosomal abnormalities or single-gene conditions were excluded from the study. Control infants were liveborn with no major birth defects, randomly selected from the same geographical populations using either birth hospital or vital records. Only 1 case or control infant was included from each multifetal pregnancy. This study received institutional review board approval at all participating sites.

To confirm eligibility, information on infants in each birth defect category was reviewed without knowledge of exposure status by clinical geneticists. In addition, case infants with heart defects were reviewed without knowledge of exposure status by a team of experts in pediatric cardiology and epidemiology of heart defects, and each case was assigned to 1 of 33 cardiac diagnostic subcategories, each of which was in turn placed into ≥1 of 9 major categories.[10] Not all types of heart defects were included in the NBDPS; those that were excluded were either not well ascertained in infancy, very rare, often related to preterm delivery (patent ductus arteriosus, patent foramen ovale), vascular defects that are not true malformations of the heart, or heart defects that were associated with chromosomal abnormalities.[11] The proportion of infants with various categories of heart defects does not reflect their relative population frequencies, because some infants with more common defects were excluded.

Extensive information regarding demographics and pregnancy exposures was collected by standardized telephone interviews with mothers of case or control infants. The interviews were conducted in English or Spanish 6 weeks to 2 years after the estimated date of delivery.[9] Infants with incomplete maternal interviews were excluded. Mothers were asked during the interview whether or not they took any of a list of medications, including Wellbutrin and Zyban. Exposure was defined as reported use of bupropion anytime between 1 month before and 3 months after conception. Women were considered unexposed if they did not use any antidepressant at any time during pregnancy. Mothers who reported having depression but who did not report use of an antidepressant during their pregnancy were excluded. Only heart defects or other birth defect categories that had at least 3 cases exposed to bupropion in the period from 1 month before to 3 months after conception were analyzed in the study.

Crude analyses were done using Pearson $\chi^2$ tests, and odds ratios (ORs) and Fisher's exact confidence limits were calculated with software (SPSS 11.0; SPSS, Inc, Chicago, IL). The following potential confounders were evaluated: maternal age (<35, ≥35 years), maternal race (non-Hispanic white, other), maternal education (≤12 years, >12 years), maternal obesity before pregnancy (body mass index <30 kg/m$^2$, ≥30 kg/m$^2$), maternal smoking and alcohol use from 1 month before to 3 months after conception, use of a dietary supplement containing folic acid from 1 month before to 1 month after conception, annual family income (<$20,000, ≥$20,000), plurality (singleton, twins and above), and parity (no previous live births, ≥1 live birth). Potential confounders were first evaluated for association with bupropion exposure and with the birth defects categories and were excluded from the logistic regression if their removal resulted in a change in risk estimate of <10%. All confounders retained in the model for any of the defects were included in the final models for all defects. Infants of women with pregestational type 1 or 2 diabetes (304 case and 32 control mothers) were excluded from adjusted analyses because of the strong association of diabetes with birth defects.

## Results

Four major categories of heart defects and 6 other categories of birth defects met the inclusion criterion of at least 3 cases exposed to bupropion in the period between 1 month before and 3 months after conception. Of 18,534 case and control mothers available for study, we excluded 276 mothers who did not complete their interviews and 6 mothers who reported depression but did not report use of any antidepressant. A total of 12,383 case infants (including 6853 diagnosed with at least 1 of the selected heart defects and 5763 diagnosed with at least 1 of the 6 categories of noncardiac defects studied) and 5869 control infants were analyzed. Among all case and control mothers, 90 (0.5%) reported use of bupropion in the 1 month before to 3 months after conception.

Characteristics of case and control mothers included in the study are pre-

sented in Table 1. Mothers of case infants were significantly more likely to be older, have a higher education, be obese, smoke early in pregnancy, and have a lower family income compared with mothers of control infants. Other characteristics, such as having type 1 or 2 diabetes prior to pregnancy, a multiple pregnancy, or at least 1 previous live birth were more frequently reported among mothers of case infants than among mothers of control infants. Pregnancy intention, on the other hand, was reported more frequently among mothers of control infants.

Seven subcategories of heart defects (which fell within 4 major categories) included at least 3 infants whose mothers reported use of bupropion early in pregnancy. Crude and adjusted ORs comparing the prevalence of case mothers to control mothers exposed to bupropion between 1 month before to 3 months after pregnancy are presented in Table 2. Factors found to influence the association between the birth defects analyzed and bupropion use were maternal race, obesity, smoking, and family income, and these factors were included in the adjusted analyses.

A statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and maternal bupropion use, based on 10 exposed pregnancies (adjusted OR, 2.6; 95% confidence interval [CI], 1.2–5.7). The main diagnoses assigned to the 10 exposed cases were coarctation of the aorta in 5 cases (1 of which also had features of a hypoplastic left heart variant), hypoplastic left heart syndrome in 3 cases, and aortic stenosis in 2 cases. Out of the 10 exposed cases with left outflow tract defects, 7 were isolated cardiovascular defects, 2 also had multiple noncardiac birth defects, and 1 infant who had coarctation of aorta was suspected to have PHACE syndrome (P, Posterior fossa abnormalities and other structural brain abnormalities; H, Hemangioma(s) of the cervical facial region; A, Arterial cerebrovascular anomalies; C, Cardiac defects, aortic coarctation and other aortic abnormalities; E, Eye Anomalies).[12] Mothers of all 10 cases reported taking Wellbutrin. None of these 10 mothers

**TABLE 1**
**Characteristics of mothers of case and control infants, National Birth Defects Prevention Study 1997–2004**

| | Bupropion | | |
|---|---|---|---|
| Characteristic | Mothers of case infants (n = 12,383), n (%) | Mothers of control infants (n = 5869), n (%) | $\chi^2$ *P* value |
| Maternal race/ethnicity | | | |
| Non-Hispanic white | 7481 (60.6) | 3525 (60.3) | .35 |
| Other | 4868 (39.4) | 2323 (39.7) | |
| Maternal age | | | |
| <35 y | 10,489 (84.7) | 5051 (86.1) | .01 |
| ≥35 y | 1894 (15.3) | 818 (13.9) | |
| Maternal education | | | |
| ≤12 y | 5546 (44.8) | 2457 (41.9) | < .001 |
| >12 y | 6826 (55.2) | 3402 (58.1) | |
| Maternal prepregnancy BMI | | | |
| Not obese (BMI <30 kg/m$^2$) | 9685 (81.3) | 4738 (84.1) | < .001 |
| Obese (BMI ≥30 kg/m$^2$) | 2223 (18.7) | 898 (15.9) | |
| Maternal smoking in the period of 1 mo before to 3 mo after conception | | | |
| 0/d | 9687 (78.3) | 4745 (80.9) | < .001 |
| 1–14/d | 1861 (15.0) | 782 (13.3) | |
| ≥15/d | 826 (6.7) | 337 (5.7) | |
| Annual family income | | | |
| <$20,000 | 3845 (33.9) | 1679 (32.0) | .01 |
| ≥$20,000 | 7507 (66.1) | 3574 (68.0) | |
| Type 1 or 2 diabetes prior to pregnancy | | | |
| No | 11,125 (97.3) | 5464 (99.4) | < .001 |
| Yes | 304 (2.7) | 32 (0.6) | |
| Maternal alcohol intake in the period of 1 mo before to 3 mo after conception | | | |
| No | 7746 (62.9) | 3677 (63.0) | .47 |
| Yes | 4572 (37.1) | 2164 (37.0) | |
| Maternal folic acid intake[a] | | | |
| No | 6124 (49.5) | 2883 (49.1) | .34 |
| Yes | 6259 (50.5) | 2986 (50.9) | |
| Plurality | | | |
| Singleton | 11,593 (93.7) | 5689 (97.0) | < .001 |
| Multiple | 775 (6.3) | 174 (3.0) | |
| Parity | | | |
| No previous live births | 5344 (43.2) | 2352 (40.1) | < .001 |
| ≥1 previous live birth | 7034 (56.8) | 3514 (59.9) | |

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**TABLE 1**
**Characteristics of mothers of case and control infants, National Birth Defects Prevention Study 1997–2004** *(continued)*

| Characteristic | Bupropion: Mothers of case infants (n = 12,383), n (%) | Bupropion: Mothers of control infants (n = 5869), n (%) | $\chi^2$ *P* value |
|---|---|---|---|
| Pregnancy intended | | | |
| No | 4448 (43.4) | 1933 (40.7) | .001 |
| Yes | 5800 (56.6) | 2821 (59.3) | |
| Exposure to bupropion[b] | | | |
| No | 11,733 (99.5) | 5626 (99.5) | .27 |
| Yes | 64 (0.5) | 26 (0.5) | |

*BMI*, body mass index.

[a] Use at any time between 1 month before and 1 month after conception; [b] Exposure to bupropion was defined as reported use at any time between 1 month before to 3 months after conception—women were considered not to have been exposed if they did not take an antidepressant at any time from 3 months before conception and through the end of pregnancy.

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reported concomitant use of a medication with known teratogenic effects, although 2 also reported use of other antidepressants (fluoxetine and paroxetine in 1 case and fluoxetine and sertraline in the other) in the first trimester. Limiting the exposure to the period of 2 months after conception, when cardiac embryogenesis is most likely to be susceptible to a teratogenic effect, reduced the number of cases exposed to 7 but did not affect the point estimate for the OR, and the association remained of borderline statistical significance (adjusted OR, 2.6; 95% CI, 1.0–6.4).

We also tested crude and adjusted associations of any congenital heart defect included in the NBDPS with maternal bupropion use, but exposure prevalence was not significantly different among cases when compared with controls (OR, 1.4; 95% CI, 0.8–2.5; n = 34). Likewise, no significant association with maternal bupropion use was observed with any of the 6 noncardiac defects categories analyzed (Table 3).

**TABLE 2**
**Associations of maternal bupropion use among infants with various categories of heart defects, National Birth Defects Prevention Study 1997–2004**

| Heart defect (n) | Crude analysis[a]: Exposed (n) | Crude analysis[a]: OR (95% CI) | Adjusted analysis[b]: OR (95% CI) |
|---|---|---|---|
| Controls (5869) | 26 | — | — |
| Conotruncal heart defects (1350) | 4 | 0.7 (0.2–1.9) | 0.9 (0.3–2.6) |
| Tetralogy of Fallot (598) | 3 | 1.1 (0.2–3.7) | 1.5 (0.4–5.1) |
| Left outflow tract heart defects (1038) | 10 | 2.2 (1.0–4.8) | 2.6 (1.2–5.7) |
| Coarctation of aorta (546) | 5 | 2.1 (0.6–5.5) | 2.6 (1.0–6.9) |
| Hypoplastic left heart (310) | 3 | 2.3 (0.4–7.5) | 2.7 (0.8–9.1) |
| Right outflow tract heart defects (1030) | 4 | 0.9 (0.2–2.6) | 1.2 (0.4–3.4) |
| Pulmonary valve stenosis (763) | 3 | 0.8 (0.2–2.8) | 1.1 (0.3–3.8) |
| Septal heart defects (3033) | 15 | 1.1 (0.5–2.2) | 1.4 (0.7–2.8) |
| Perimembranous VSD (1214) | 6 | 1.1 (0.4–2.8) | 1.2 (0.5–3.4) |
| ASD secundum (1320) | 5 | 0.9 (0.3–2.3) | 1.1 (0.4–3.0) |
| ASD nos (430) | 3 | 1.6 (0.3–5.2) | 2.2 (0.6–7.5) |
| All groups of heart defects in NBDPS (6853) | 34 | 1.1 (0.7–1.9) | 1.4 (0.8–2.5) |

*ASD*, atrial septal defects; *CI*, confidence interval; *NBDPS*, National Birth Defects Prevention Study; *nos*, not otherwise specified; *OR*, odds ratio; *VSD*, ventricular septal defects.

[a] Fisher's exact CI; [b] Adjusted for maternal race, obesity, smoking, and family income—cases and controls with preexisting type 1 or 2 diabetes in the mother were excluded.

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## Comment

A relatively large number of cases with congenital heart defects among mothers exposed to bupropion was noted among both prospective and retrospective reports to the Bupropion Pregnancy Registry.[7] Although no comparable reference group was available to permit statistical assessment of this observation, these results raised concern that maternal bupropion treatment early in pregnancy might be associated with an increased risk of congenital heart defects. We used data from a population-based case-control study to test this hypothesis. We found a positive association with maternal bupropion use during pregnancy among infants with left outflow tract heart defects but not among infants with other types of heart defects. When we analyzed infants with any ≥1 of the major heart defects included in NBDPS as a group, we found no association with reported maternal use of bupropion early in pregnancy.

Our study has several important strengths. It is large and population based, uses consistent case definitions, and incorporates information on many potential confounders. The study sample provided adequate statistical power to evaluate the relationship between bupropion exposure and the risk for several individual types of cardiovascular birth defects.

However, the small number of exposed cases for each defect category remains a limitation. Because of the small

**TABLE 3**
**Associations of maternal bupropion use among infants with various categories of birth defects not involving the heart, National Birth Defects Prevention Study 1997–2004**

| | Crude analysis[a] | | | Adjusted analysis[b] |
|---|---|---|---|---|
| Birth defect (n) | Controls[c] (no. exposed) | No. of exposed cases | OR (95% CI) | OR (95% CI) |
| Neural tube defects (1043) | 5869 (26) | 4 | 0.9 (0.2–2.5) | 1.3 (0.4–3.9) |
| Cleft lip with or without palate (1552) | 5735 (24) | 7 | 1.1 (0.4–2.6) | 1.3 (0.4–3.9) |
| Cleft palate (824) | 5735 (24) | 4 | 1.2 (0.3–3.4) | 1.2 (0.4–3.6) |
| Hypospadias, second or third degree (1147) | 2951 (12) | 9 | 1.9 (0.7–5.0) | 2.3 (0.9–5.9) |
| Limb deficiency (648) | 5869 (26) | 3 | 1.0 (0.2–3.4) | 1.4 (0.4–4.8) |
| Gastroschisis (611) | 5869 (26) | 3 | 1.1 (0.2–3.7) | 1.4 (0.4–5.1) |

*CI*, confidence interval; *OR*, odds ratio.

[a] Fisher's exact CI; [b] Adjusted for maternal race, obesity, smoking, and family income—cases and controls with preexisting type 1 or 2 diabetes in the mother were excluded; [c] Number of controls is different for oral clefts and hypospadias, because data on oral clefts from Utah in 2003 were not available and only male control infants were included for infants with hypospadias.

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number of cases exposed to bupropion overall, we were unable to stratify our analyses by type of bupropion exposure (Wellbutrin vs Zyban), which would have enabled us to deal with confounding by indication (depression vs smoking cessation). We cannot rule out the possibility that the association we observed with left outflow tract heart defects is actually related to depression, rather than to bupropion use, since all women were taking bupropion for depression. However, the fact that previous studies of maternal serotonin reuptake inhibitor use have not shown an association with this type of heart defect[13] makes this explanation unlikely. Furthermore, because data on dosage were unavailable, we were unable to evaluate a potential dose-response relationship. The use of bupropion was determined by maternal self-reports and was not validated through other sources, so the influence of recall bias on the results is difficult to assess. Although we calculated an overall OR for all heart defect categories combined (Table 2), this estimate may not be comparable to overall estimates from other studies, because NBDPS collects data on selected major heart defects rather than all heart defects or heart defects in general.

The magnitude of the association with left outflow tract heart defects suggests a possible doubling of risk over baseline if the association is not due to chance or methodological issues such as bias or confounding. Replication of these findings in other studies that address such methodological considerations are warranted before inferences about a possible causal relationship between medication use and the occurrence of this type of heart defect can be made with any degree of confidence. Even if there were a 2-fold increased risk for left outflow tract heart defects, the absolute risk of a cardiovascular malformation in the child of a pregnant woman who takes bupropion during the first trimester would be low. Based on an estimated prevalence for left outflow tract heart defects of 0.82/1000 live births in the metropolitan Atlanta, GA, population in 1998–2005,[14] our findings are compatible with an absolute risk following first-trimester maternal bupropion treatment of 2.1/1000 births.

In their retrospective cohort study of health care claims records, Cole et al[8] observed 13 infants with congenital heart defects whose mothers had received bupropion prescriptions in the first trimester of pregnancy, a frequency that was not significantly increased when compared with infants whose mothers had received prescriptions for other antidepressants or infants whose mothers received bupropion prescriptions outside the first trimester. Five of the 13 infants with congenital heart defects born to women who had received prescriptions for bupropion during the first trimester and 6 of 57 infants of women who had received prescriptions for other antidepressants during the first trimester in the study of Cole et al[8] had left outflow tract heart defects, which are estimated to account for about 10% of all heart defects in the general population.[14] Based on the data reported in the study by Cole et al,[8] we calculated a crude risk ratio for bupropion use compared with use of the other antidepressants of 3.2 (95% CI, 1.0–10.6), a value similar to that observed in our study.

A family history of congenital heart defects was not reported for any of the 10 infants with left outflow tract defects whose mothers reported taking bupropion early in pregnancy in our study. Familial clustering of this group of heart defects has been suggested in the literature,[15] indicating a genetic component in their etiology. Of course, this does not preclude the involvement of teratogenic factors as well in a complex and probably etiologically heterogeneous disorder such as congenital heart defects.

We found no increased odds of maternal bupropion use early in pregnancy among infants with neural tube defects, cleft lip with or without cleft palate, cleft palate alone, second- or third-degree hypospadias, or gastroschisis (Table 3). Maternal bupropion exposure in pregnancy was not found to be associated with other major birth defects in the retrospective cohort study of Cole et al[8] or

in a small prospective cohort study performed through a teratogen information service.[16] Similarly, the frequency of malformations was not increased among the offspring of rats or rabbits treated during pregnancy with the equivalent of 19–56 or 3–19 times the maximum human therapeutic dose of bupropion.[17] It is unclear how carefully the pups in this study were examined to determine the presence or absence of heart defects.

A critical question is whether the association we observed with left outflow tract heart defects is biologically plausible. This question cannot currently be addressed, because so little is known about the effect of bupropion treatment on embryonic development in general or on cardiac morphogenesis specifically.

Our results are based on exploratory analyses of a case-control study; therefore, our findings are not conclusive. Further studies are needed to confirm our findings in other datasets and to assess whether the risk extends to other birth defects, as well as to elucidate the underlying pathogenic mechanism(s). These findings, along with recent evidence related to the effects of serotonin reuptake inhibitors in pregnancy[13,18-23] present health care providers with a dilemma regarding choice of antidepressant medications in pregnancy. It is important to note that the absolute risk for left outflow tract heart defects we found associated with bupropion exposure is small. Nevertheless, risks and benefits of antidepressant medications need to be considered on a case-by-case basis and clearly presented to women who are pregnant or planning pregnancy so that they can make informed decisions in consultation with their physicians. ■

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