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MATERNAL ANTIHYPERTENSIVE MEDICATION USE AND CONGENITAL HEART DEFECTS: UPDATED RESULTS FROM THE NATIONAL BIRTH DEFECTS PREVENTION STUDY

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Abstract

Previous National Birth Defects Prevention Study (NBDPS) findings from 1997–2003 suggested that maternal antihypertensive use was associated with congenital heart defects (CHDs). We re-examined associations between specific antihypertensive medication classes and specific CHDs with additional NBDPS data from 2004–2011. After excluding mothers missing hypertension information or who reported pre-gestational diabetes, a multiple birth, or antihypertensive use but no hypertension, we compared self-reported maternal exposure data on 10,625 CHD cases and 11,137 non-malformed controls. We calculated adjusted odds ratios [95% confidence intervals] to estimate risk of specific CHDs associated with antihypertensive use during the month before conception through the third month of pregnancy, controlling for maternal age, race/ethnicity, body mass index, first trimester cigarette smoking, and NBDPS site. Overall, 164 (1.5%) case mothers and 102 (0.9%) control mothers reported early pregnancy antihypertensive use for their hypertension. We observed increased risk of four CHD phenotypes, regardless of antihypertensive medication class reported: coarctation of the aorta (2.50 [1.52–4.11]), pulmonary valve stenosis (2.19 [1.44–3.34]), perimembranous ventricular septal defect (1.90 [1.09–3.31]), and secundum atrial septal defect (1.94 [1.36–2.79]). The associations for these phenotypes were statistically significant for mothers who reported β-blocker use or renin-angiotensin system blocker use; estimates for other antihypertensive medication classes were generally based on fewer exposed cases and were less stable but remained elevated. Our results support and expand upon earlier

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Conflicts of Interest/Disclosures

The authors report no conflicts of interest.

NBDPS findings that antihypertensive medication use may be associated with increased risk of specific CHDs, although we cannot completely rule out confounding by underlying disease characteristics.

Keywords

hypertension; antihypertensive; pregnancy; congenital heart defects; National Birth Defects Prevention Study

Introduction

Chronic hypertension complicates approximately 2% of pregnancies[1], but the effects of antihypertensive medication use on the developing fetus are not well understood. There is relatively consistent evidence that maternal hypertension, regardless of its treatment, is associated with a moderately increased risk of congenital heart defects (CHDs)[2,3,4,5], but the question remains as to whether early pregnancy antihypertensive use is also independently associated with increased risk of CHDs. Most relevant studies have either analyzed antihypertensive use overall[2,6,7] or CHDs overall[3,7,8,9,10], with mixed results. However, CHDs are a diverse group of individual defects with complex developmental mechanisms that may be etiologically distinct. Similarly, classes of antihypertensive medications represent different mechanisms of action, which may affect fetal development differently.

In an earlier analysis using data from the National Birth Defects Prevention Study (NBDPS), we investigated associations between specific antihypertensive medication classes and specific CHDs.[11] We observed positive associations between β-blockers and pulmonary valve stenosis (PVS) and secundum atrial septal defects (ASD2), centrally-acting antiadrenergic agents and Ebstein malformation, and diuretics and ASD2. Our analysis included births from 1997–2003 but was limited by small numbers of exposed cases; we only investigated associations between specific antihypertensive classes and four CHD phenotypes. The current NBDPS dataset now includes births through 2011. Using this dataset, we conducted a more detailed analysis of the association between specific CHDs and maternal use of antihypertensive medication classes.

Methods

The NBDPS was a multi-site, population-based case-control study to investigate risk factors for more than 30 major birth defects.[12] We analyzed data on NBDPS controls and cases with a CHD from 10 study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, Utah) with estimated delivery dates (EDDs) during October 1997-December 2011. A mother was eligible for the NBDPS if she had legal custody of her child, had not previously participated in the study, was not incarcerated, and could complete the interview in English or Spanish. Each study site and the Centers for Disease Control and Prevention obtained Institutional Review Board approval for the study and participants provided informed consent.

Controls were non-malformed live births randomly selected from birth certificates or hospital discharge records in each study site. Medical record abstractors ascertained all cases with an eligible defect within the study time period and geographic areas. Clinical geneticists reviewed all cases to determine eligibility. CHD cases required confirmation via echocardiogram, surgical report, cardiac catheterization, or autopsy; cases with a known etiology (e.g. recognized single gene disorder, chromosomal abnormality) were excluded. Cases were classified according to a structured protocol that incorporated cardiac phenotype, complexity, and presence of extra-cardiac defects.[13] We enrolled cases of each CHD phenotype throughout the entire study, with the exception of ventricular septal defects (VSDs). Muscular and unspecified VSDs were ascertained during the first study year, and all other VSDs were ascertained through 2005 EDDs. For 2006–2011 EDDs, VSDs were only ascertained if another eligible CHD was also present ("passive ascertainment").

Trained interviewers collected data via telephone interviews between 6 weeks and 24 months after the EDD; 65% and 67% of eligible control and case mothers, respectively, participated.[12] The interview included questions on maternal demographics, pregnancy history, behaviors, and medication use during the three months before pregnancy until delivery. Specifically, interviewers asked about diagnosis, timing, and treatment of "high blood pressure" for mothers of infants with 1997–2005 EDDs and "high blood pressure, toxemia, pre-eclampsia or eclampsia" for mothers of infants with 2006–2011 EDDs. Mothers reported the name, timing, and frequency of antihypertensive medication used during the three months before pregnancy until delivery.

We considered a mother exposed to hypertension if she reported having hypertension during the index pregnancy, and exposed to antihypertensive medication if she reported use any time during the month before pregnancy through the third month of pregnancy ("early pregnancy"). We also analyzed a separate group of hypertensive mothers who only reported antihypertensive use during the second or third trimester ("late pregnancy"). We coded medications using the Slone Epidemiology Center Drug Dictionary (Boston, MA). We categorized medications into drug classes based on mechanism of action: centrally-acting antiadrenergic agents, β-blockers, renin-angiotensin system blockers (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers), calcium channel blockers, diuretics, and direct vasodilators.

Due to the known strong association between pre-gestational diabetes and CHDs[14], we excluded mothers who reported pre-existing type 1 or type 2 diabetes from our analysis (cases=441, controls=83). We also excluded mothers with a multiple birth (cases=830, controls=352), who were missing information on hypertension or antihypertensive use (cases=289, controls=306), or who reported antihypertensive medication use but not hypertension (cases=71, controls=56). Our exclusions totaled 1,518 case and 692 control mothers, with overlap across exclusion categories. Among cases, we excluded passively ascertained VSDs and most complex patterns of CHDs (n=441). Complex patterns of CHDs are those with poorly-defined phenotypes characterized by independent defects in multiple cardiac structures, such as one case of truncus arteriosus with atrial septal defect and coarctation of the aorta (CoA), or another case with double outlet right ventricle, ASD,

VSD, pulmonic stenosis, and straddling tricuspid valve. We did, however, include single ventricle and heterotaxy cases, which we considered complex but well-defined.

We used unconditional logistic regression (SAS 9.4 [Cary, NC]) to estimate crude odds ratios (cORs) and adjusted ORs (aORs) and their 95% confidence intervals (CIs) representing the relative risk of a CHD among mothers reporting early pregnancy antihypertensive use overall, by medication class, and, where sample size permitted, by individual medication. To assess potential confounding by the underlying hypertension, we also estimated risk of CHDs associated with late pregnancy antihypertensive initiation and untreated hypertension. For our main analyses, the non-exposed group was normotensive mothers who did not report antihypertensive use during pregnancy. To further isolate the effect of antihypertensive medication from the effect of the underlying hypertension, we conducted a sub-analysis using untreated hypertensive mothers as the non-exposed group.

We constructed a logistic regression model based on a priori covariate selection, following our literature review of potential confounders. For case groups with at least five exposed cases, we adjusted for maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); maternal age in years at delivery (<20, 20–34, ≥35); maternal pre-pregnancy body mass index (BMI) (underweight: <18.5, normal: 18.5–24, overweight: 25–29, obese: ≥30); early pregnancy maternal cigarette smoking (any, none); and study site. For groups with three or four exposed cases, we estimated cORs and exact 95% CIs.

To reduce heterogeneity, we conducted a sub-analysis restricted to cases with a single CHD or a well-recognized combination of defects that are considered essentially a single CHD (e.g. tetralogy of Fallot, hypoplastic left heart syndrome), referred to as “simple” cases. We also repeated the same logistic regression analyses restricting each exposure category to mothers who reported only one medication class during early pregnancy, to better isolate the effects of individual classes. Finally, we stratified our results by time period (EDDs 1997–2003 vs. 2004–2011) to determine whether our current findings confirmed our previous findings.[11]

Results

After exclusions, we analyzed interview data from mothers of 11,137 controls and 10,625 CHD cases (Figure 1). In our study, cases were more likely than controls to be at least 35 years old, overweight or obese, report early pregnancy cigarette smoking, and have an EDD during 1997–2003 (Table 1).

Overall, untreated hypertension was more prevalent among case (9.2%) than control (7.6%) mothers, as was early (1.5% vs. 0.9%) and late (1.1% vs. 0.6%) pregnancy antihypertensive use (Table 2). In adjusted analyses, early pregnancy antihypertensive use was associated with increased risk of seven distinct CHDs; we observed statistically significant estimates for CoA, PVS, Ebstein anomaly, perimembranous VSD (VSD-PM), and ASD2, ranging from 1.90 (95% CI 1.09–3.31) for VSD-PM to 3.89 (95% CI 1.51–10.06) for Ebstein anomaly. Estimates for tetralogy of Fallot and hypoplastic left heart syndrome were slightly elevated, but CIs intersected the null. Except for Ebstein anomaly, both untreated

hypertension and late pregnancy antihypertensive use were also significantly associated with increased risk of the same defects, with estimates ranging from 1.26 (95% CI 1.02–1.56) for VSD-PM to 1.43 (95% CI 1.15–1.79) for CoA among untreated hypertensive women, and from 1.85 (95% CI 1.02–3.37) for VSD-PM to 2.61 (95% CI 1.75–3.89) for ASD2 among late pregnancy antihypertensive users. Ebstein anomaly risk was elevated, but non-significant, among untreated hypertensive women; too few cases were exposed to late pregnancy antihypertensive use to calculate an estimate. We also observed elevated cORs for antihypertensive use and six defects (heterotaxy, truncus arteriosus, atrioventricular septal defect, total anomalous pulmonary venous return, pulmonary atresia, and muscular VSD), but all were non-significant.

We included centrally-acting antiadrenergics, β-blockers, renin-angiotensin system blockers, calcium channel blockers, and diuretics in our analysis of antihypertensive use by class; other antihypertensive classes were each reported by fewer than three case mothers. Early pregnancy use of each of the classes analyzed was associated with increased risk of CHDs overall (Table 3). Specifically, we observed elevated odds ratios for PVS, VSD-PM, and ASD2 across all medication classes. ORs for CoA were increased among mothers who reported centrally-acting antiadrenergic, β-blocker, or renin-angiotensin system blocker use, but there were not enough exposed cases to calculate risk associated with calcium channel blockers or diuretics. Some estimates were based on small numbers and did not reach statistical significance; however, both β-blockers and renin-angiotensin system blockers were significantly associated with increased risk of PVS (aOR 3.03 95%, CI 1.68–5.46 and aOR 3.74, 95% CI 1.39–10.17, respectively), VSD-PM (aOR 4.13, 95% CI 1.82–9.37 and aOR 6.58, 95% CI 1.55–27.97, respectively), and ASD2 (aOR 2.35, 95% CI 1.37–4.04 and aOR 3.25, 95% CI 1.29–8.20, respectively). B-blockers were also significantly associated with CoA (aOR 2.61, 95% CI 1.25–5.45), as were diuretics with ASD2 (aOR 3.22, 95% CI 1.30–7.99). Due to sparse data, medication-specific analyses were limited to methyldopa, a centrally-acting antiadrenergic, and labetalol, a non-selective β-blocker. Most cases (94.7%) and controls (92.8%) who reported centrally-acting antiadrenergic use reported methyldopa, producing similar results for both groups. Labetalol users represented 43.8% and 42.5% of cases and controls, respectively, who reported early pregnancy β-blocker use. Although the numbers of exposed cases were small and some confidence intervals were wide, labetalol was also associated with increased risk of the same defects associated with β-blocker use overall (Table S1).

Our sub-analysis comparing antihypertensive users to untreated hypertensive mothers generally reiterated the previously-observed associations between all antihypertensive medication classes and CoA, PVS, VSD-PM, and ASD2 (Table S2). The same patterns persisted when we restricted to simple defects only (data not shown).

Among the 102 control and 164 case mothers who reported any antihypertensive use during early pregnancy, 21 controls and 47 cases reported multiple antihypertensive medication classes during that time period. Case and control mothers reported 21 different combinations of antihypertensive medication classes during early pregnancy; the most prevalent combinations were β-blockers and centrally-acting antiadrenergics (controls=4, cases=11), β-blockers and diuretics (controls=1, cases=9), and centrally-acting

antiadrenergics and renin-angiotensin system blockers (controls=4, cases=4) (data not shown). In our sub-analysis of mothers who reported only one antihypertensive medication class during early pregnancy, most associations remained elevated, but only those for exclusive β-blocker use and CoA (aOR 2.47, 95% CI 1.08–5.69) or VSD-PM (aOR 3.39, 95% CI 1.19–9.70) and for exclusive centrally-acting antiadrenergic agent use and CoA (aOR 2.78, 95% CI 1.13–6.82) remained statistically significant (Table S3).

Overall, our stratified analysis of data from mothers with EDDs during 2004–2011 supports our previously published results using data from mothers with EDDs during 1997–2003 (Table 4). We continued to observe associations between early pregnancy antihypertensive use (any class) and increased risk of CHDs overall, PVS, CoA, ASD2, and VSD-PM. We were unable to estimate an association between antihypertensive use and Ebstein anomaly, as there was only one exposed case mother among EDDs after 2003. Regarding specific medication classes, previously observed associations with early pregnancy β-blocker use persisted for PVS, CoA, and ASD2 (data not shown).

Discussion

We observed that both maternal hypertension and maternal antihypertensive use during pregnancy were associated with increased risk of CHDs. Across almost every analysis of untreated hypertension, early pregnancy antihypertensive use, and late pregnancy antihypertensive use, we observed increased risks for a consistent set of CHDs: PVS, VSD-PM, ASD2, and CoA. Hypertensive mothers who reported antihypertensive use had higher risk of these CHDs than untreated mothers. The most compelling evidence was for associations between early pregnancy β-blocker or renin-angiotensin system blocker use and these CHDs, based on risk estimates ranging from 2.35 to 6.58. We also observed two-fold or greater increases in risks of other defects associated with other specific antihypertensive classes, but generally with less precision.

These results support our earlier NBDPS findings for early pregnancy antihypertensive use and PVS, CoA, and ASD2.[11] In both analyses, we observed increased risk of these CHDs among early pregnancy β-blocker users, specifically. Previously, we observed non-significantly increased risk of VSD-PM among antihypertensive users; in our current study, we observed a stronger, statistically significant association, again among β-blocker users. When VSD and ASD were grouped together, Lennestal et al. reported increased risk associated with any antihypertensive use during early pregnancy, but did not distinguish between antihypertensive classes.[7] This same study and another Swedish cohort reported increased risk of CHDs overall among β-blocker users.[10] A more recent study reported increased risk of VSD, ASD, and left-sided CHDs among antihypertensive users who had chronic hypertension with superimposed preeclampsia, but not among women with treated chronic hypertension alone.[6] This result may indicate that the severity of the underlying hypertension affects risk of these CHDs, more than the medication used, but we are unable to make this distinction among hypertensive mothers in the NBDPS.

We do not know of any other publications reporting the risk of specific CHDs associated with early pregnancy renin-angiotensin system blocking agent use. One high-profile paper

by Cooper et al. reported an increased risk of any CHD associated with first trimester ACE inhibitor use, compared to other antihypertensives,[8] which was not replicated in two subsequent studies.[3,7] Our study did find an association between renin-angiotensin system blocking agent use (including ACE inhibitors) and CHDs overall, as well as with specific CHD phenotypes. This finding persisted when compared to normotensive mothers as well as when compared to untreated hypertensive mothers. Unlike the Cooper study, however, we found that increased risk of CHDs was not limited to renin-angiotensin system blockers, and that the ORs observed for other medication classes were similarly elevated.

We observed that antihypertensive medications were associated with several distinct CHD phenotypes, which likely involve a range of genetic determinants of early patterning.[15] However, the four defects with the most consistently observed increased ORs—VSD-PM, ASD2, PVS, and CoA—have been hypothesized to stem from abnormal intracardiac blood flow.[16] The increased blood pressure variability that characterizes hypertension may lead to this type of abnormal blood flow, as may antihypertensives acting directly on the fetus. Many antihypertensives—including β-blockers and ACE inhibitors—cross the placenta, potentially inducing fetal hypotension, which may impact fetal heart development.[17,18]

Most of our statistically significantly elevated ORs involved use of β-blockers and renin-angiotensin system blockers. These two classes have different mechanisms of action and their unifying feature—that they work to lower blood pressure—is not unique to these medications. We did observe increased ORs for the same CHDs among women who used other medication classes, but those estimates were generally not statistically significant. In our main analysis, medication exposure categories were not mutually exclusive, and more than one-quarter of our exposed population reported multiple antihypertensive classes during early pregnancy. When restricted to mothers who reported only one type of antihypertensive during early pregnancy, the number of exposed cases for specific CHD phenotypes became small, particularly for renin-angiotensin system blockers, calcium channel blockers, and diuretics, making it difficult to draw conclusions on the effects of individual medication classes.

We also had limited power to analyze specific medications within classes. Methyldopa is the traditionally recommended therapy for pregnant women with chronic hypertension,[19] and we only observed modest, non-significantly increased ORs for CoA, PVS, VSD-PM, and ASD. Within the β-blocker class, labetalol is also generally believed to be safe to use during pregnancy.[20] However, the increased risks we observed between β-blockers overall and CHDs were present among labetalol users, as well. Although we did not directly compare risks associated with labetalol use to those of other types of β-blockers, our results do not suggest that labetalol is safer with respect to CHD risk than other β-blockers.

Initiating antihypertensive use in the second or third trimester was associated with the same CHDs as early antihypertensive use. This may reveal that the underlying hypertensive disorder, which may have been present in some form but untreated during the critical period of organogenesis in early pregnancy, is the true driver of CHD risk. Indeed, our study confirmed others' findings that untreated chronic hypertension is also independently associated with CHDs.[2,3,6] We attempted to control for confounding by indication by

conducting a subanalysis restricted to women with hypertension. We observed that the associations between PVS, VSD-PM, and ASD2 and both β-blockers and renin-angiotensin system blockers persisted. This supports our hypothesis that the risk of CHDs associated with these antihypertensive medications is above and beyond the risk associated with the underlying hypertension. However, there are likely important differences in the underlying disease of untreated and treated hypertensive women and that treated chronic hypertension is more severe than untreated chronic hypertension. Furthermore, we have incomplete data on type of hypertension in pregnancy or when that hypertension was diagnosed, which could lead to misclassification, particularly of women categorized as having untreated chronic hypertension. Chronic hypertension only accounts for approximately 20% of all hypertensive disorders in pregnancy[21], meaning that many of the women included in our analysis as having untreated hypertension likely did not have chronic hypertension. Thus, despite our best attempt to control for underlying hypertension, we cannot entirely rule out confounding by indication.

Among the many strengths of our study are its size, population base, and standardized interview protocol. Interviewers gathered detailed information on specific medications used during the critical window of fetal heart development. NBDPS investigators meticulously reviewed eligible cases, ensuring accuracy and the ability to differentiate between specific CHD phenotypes. Yet even in our large study, both antihypertensive use and individual CHDs were rare, limiting our power to analyze all medication classes and phenotypes. Additionally, we did not collect detailed information on the type of hypertension, blood pressure measurements, or medication dosage, making it difficult to account for potential confounding by indication. Recall accuracy is another concern, because all exposure data is based on maternal report up to 24 months post-EDD. However, studies indicate maternal recall of hypertensive disorders in pregnancy is “moderately” valid, with generally high sensitivity and specificity for reported antihypertensive medication use.[22,23] It is possible that there was differential exposure recall by case and control mothers, but given that our study focused on a chronic condition with a daily treatment regimen, we believe it is unlikely that control mothers would substantially under-report antihypertensive use. Finally, we conducted many statistical tests and some of our statistically significant findings may be due to chance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspectives

Our study suggests that hypertensive women are at a higher risk of giving birth to an infant with certain CHDs, specifically PVS, VSD-PM, ASD2, and CoA. With our large sample size and detailed case ascertainment protocol, we were better able than previous studies to assess associations between specific antihypertensive classes and CHD phenotypes, but our results do not suggest any strong class-specific effects. Because we were neither able to distinguish among specific types of hypertension nor measure hypertension severity, our findings of increased risks of certain CHDs among various antihypertensive classes may be explained by the underlying disease characteristics. Studies that can better control for confounding by indication are needed to determine the clinical relevance of our results. Until then, our findings should be considered hypothesis-generating and interpreted with caution.

Novelty and Significance

1. What is new?

- Our large, population-based study examined associations between early pregnancy antihypertensive medication use and specific CHDs.

2. What is relevant?

- Chronic hypertension affects 2% of U.S. pregnancies; little is known about the effects of antihypertensive use on the developing heart.
- With their different mechanisms of action, it is important to evaluate class-specific effects of antihypertensives on CHD risk.

3. Summary:

- Early pregnancy antihypertensive use, regardless of medication class, later pregnancy antihypertensive initiation, and or untreated hypertension were all associated with increased risk of coarctation of the aorta, pulmonary valve stenosis, perimembranous ventricular septal defects, and secundum atrial septal defects.

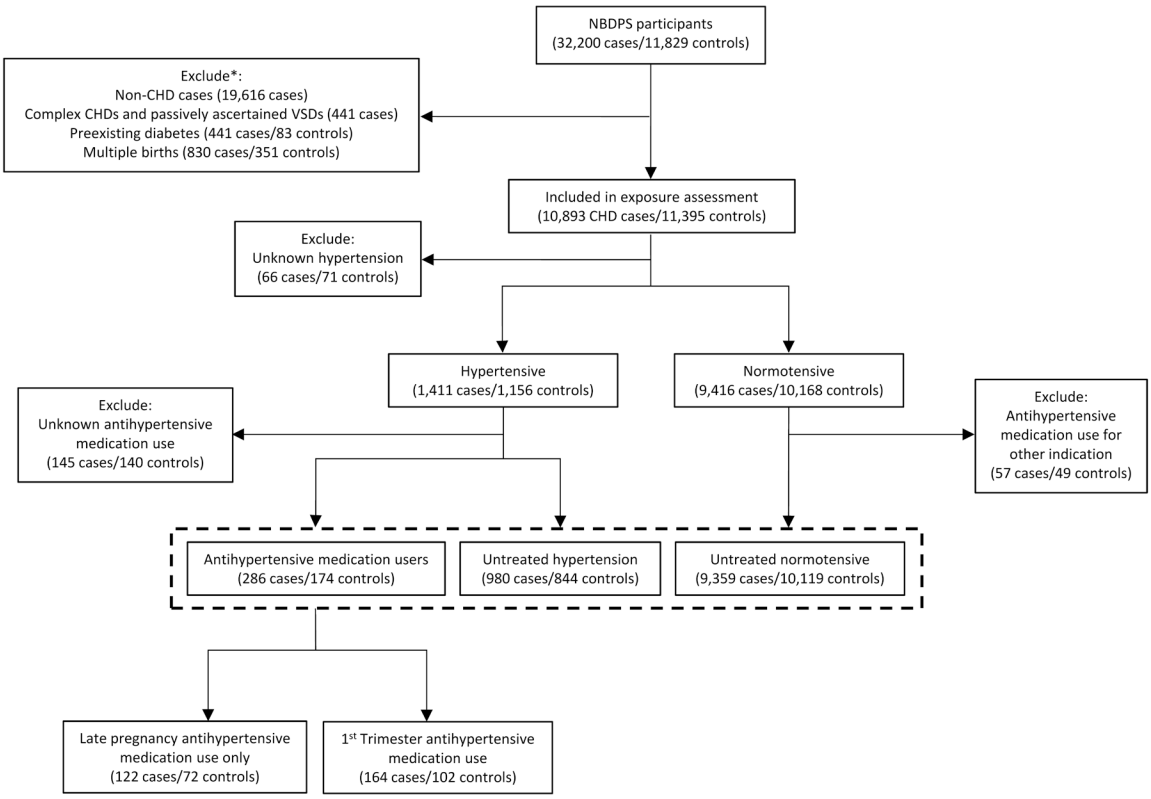

Figure 1.

Study population and exclusions, National Birth Defects Prevention Study, 1997–2011. Cases and controls included in study (n=10,625 cases, 11,137 controls), by exposure status, are surrounded by dotted line.

*Not mutually exclusive exclusion categories.

Table 1.

Maternal characteristics of included study participants, by case/control status, National Birth Defects Prevention Study, 1997–2011. Data are presented as n (%).

Characteristic	Controls	CHD Cases	*P*-value
Overall	11,137	10,625	
Age at Delivery			0.015
<20 years	1,114 (10.0)	971 (9.1)	
20–34 years	8,499 (76.3)	8,089 (76.1)	
≥35 years	1,524 (13.7)	1,565 (14.7)	
Race/Ethnicity			0.164
Non-Hispanic White	6,440 (57.9)	6,225 (58.6)	
Non-Hispanic Black	1,214 (10.9)	1,181 (11.1)	
Hispanic	2,755 (24.8)	2,496 (23.5)	
Other	722 (6.5)	723 (6.8)	
Pre-pregnancy BMI			<0.001
Underweight	571 (5.4)	560 (5.5)	
Normal	5,744 (53.8)	5,090 (50.0)	
Overweight	2,420 (22.7)	2,467 (24.3)	
Obese	1,940 (18.2)	2,058 (20.2)	
First Trimester Smoking	1,975 (17.9)	2,084 (19.8)	<0.001
Year of EDD			<0.001
1997–2003	4,778 (42.9)	4,872 (45.9)	
2004–2011	6,359 (57.1)	5,753 (54.2)	

Abbreviations: BMI, body mass index, EDD, estimated date of delivery

Table 2.

Association between hypertension and antihypertensive medication use and CHDs, by timing of medication use, NBDPS, 1997–2011.

		Early Pregnancy Antihypertensive Medication Use		Untreated Hypertension		Late Pregnancy Antihypertensive Medication Initiation	
Defect	**Unexposed**	**Exposed**	**OR* (95% CI)**	**Exposed**	**OR* (95% CI)**	**Exposed**	**OR* (95% CI)**
Controls – n (%)	10,119 (90.9)	102 (0.9)		844 (7.6)		72 (0.6)	
Any CHD – n (%)	9,359 (88.1)	164 (1.5)	1.59 (1.23–2.05)	980 (9.2)	1.23 (1.11–1.36)	122 (1.1)	1.78 (1.32–2.40)
Heterotaxy	283	3	1.05 (0.21–3.19)	15	0.65 (0.38–1.12)	4	1.99 (0.52–5.37)
Conotruncal defects							
Truncus arteriosus	94	3	3.17 (0.63–9.80)	12	1.39 (0.73–2.63)	1	-
Tetralogy of Fallot	956	13	1.14 (0.63–2.06)	102	1.32 (1.05–1.64)	9	1.18 (0.56–2.48)
D-transposition of the great arteries	653	3	0.46 (0.09–1.38)	52	0.93 (0.68–1.26)	3	0.65 (0.13–1.97)
DORV-TGA	129	0	-	14	1.41 (0.80–2.48)	1	-
Conoventricular VSD†	89	1	-	11	1.58 (0.83–3.00)	0	-
AVSD	281	3	1.06 (0.21–3.22)	29	1.25 (0.84–1.86)	3	1.50 (0.30–4.61)
Total APVR	258	3	1.15 (0.23–3.51)	15	0.71 (0.41–1.23)	3	1.63 (0.33–5.02)
LVOT defects							
Hypoplastic left heart syndrome	552	8	1.09 (0.47–2.52)	44	0.95 (0.69–1.31)	2	-
Coarctation of the aorta	891	20	2.50 (1.52–4.11)	105	1.43 (1.15–1.79)	13	2.31 (1.26–4.24)
Aortic stenosis	384	4	1.03 (0.28–2.75)	48	1.32 (0.95–1.83)	6	1.93 (0.76–4.88)
RVOT defects							
Pulmonary atresia	208	4	1.91 (0.51–5.11)	17	0.87 (0.51–1.49)	1	-
Pulmonary valve stenosis‡	1,191	33	2.19 (1.44–3.34)	148	1.42 (1.17–1.72)	17	1.93 (1.10–3.37)
Tricuspid atresia	149	0	-	6	0.44 (0.18–1.08)	0	-
Ebstein anomaly	141	5	3.89 (1.51–10.06)	15	1.30 (0.76–2.25)	2	-
Septal defects							
Perimembranous VSD†	1,110	19	1.90 (1.09–3.31)	130	1.26 (1.02–1.56)	15	1.85 (1.02–3.37)
Muscular VSD§	171	1	-	6	0.45 (0.18–1.10)	3	2.23 (0.34–11.6)
Secundum ASD	2,307	52	1.94 (1.36–2.79)	272	1.35 (1.15–1.57)	45	2.61 (1.75–3.89)
Single ventricle	135	1	-	10	0.82 (0.41–1.63)	1	-

Abbreviations: CHD, congenital heart defect; DORV-TGA, double outlet right ventricle with transposition of the great arteries; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; APVR, anomalous pulmonary venous return; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; ASD, atrial septal defect.

*For CHD phenotypes with 3–4 exposed cases, calculated crude OR and exact CI; for 5+ exposed cases, adjusted for maternal race/ethnicity, BMI, age, early pregnancy smoking, and study site.

†Only includes VSDs actively ascertained prior to EDD 2006 (n=5882 controls). VSDs collected for EDDs 2006–2011 in association with another defect are counted under the associated defect(s).

‡Excludes CA cases and controls with EDD prior to 2002 (n=9801 controls).

§Only includes VSDs actively ascertained prior to EDD 1999 (n=637 controls). VSDs collected for EDDs 1999–2011 in association with another defect are counted under the associated defect(s).

Table 3.

Association between early pregnancy antihypertensive medication use, by class*, and congenital heart defects, NBDPS, 1997–2011.

		Centrally-Acting Antiadrenergics		β-Blockers		Renin-Angiotensin System Blockers		Calcium Channel Blockers		Diuretics	
Defect†	Unexp	Exp	OR (95% CI)‡	Exp	OR (95% CI)‡	Exp	OR (95% CI)‡	Exp	OR (95% CI)‡	Exp	OR (95% CI)‡
Controls	10,119	42		40		11		11		13	
Any CHD	9,359	57	1.35 (0.89–2.04)	73	1.84 (1.25–2.72)	32	2.89 (1.41–5.91)	18	1.41 (0.65–3.05)	26	2.06 (1.02–4.13)
Heterotaxy	283	3	2.55 (0.50–8.07)	1	-	2	-	0	-	1	-
Conotruncal defects											
Tetralogy of Fallot	956	4	1.01 (0.26–2.79)	2	-	1	-	2	-	3	2.44 (0.45–8.91)
D-transposition of the great arteries	653	3	1.11 (0.22–3.48)	1	-	0	-	0	-	0	-
Total APVR	258	1	-	3	2.94 (0.58–9.33)	0	-	0	-	0	-
LVOT defects											
Hypoplastic left heart syndrome	552	0	-	4	1.83 (0.48–5.10)	1	-	3	5.00 (0.89–18.99)	2	-
Coarctation of the aorta	891	6	1.94 (0.81–4.63)	9	2.61 (1.25–5.45)	3	3.10 (0.55–11.75)	0	-	2	-
RVOT defects											
Pulmonary atresia	208	1	-	3	3.65 (0.72–11.6)	1	-	0	-	1	-
Pulmonary valve stenosis§	1,191	11	1.75 (0.86–3.56)	17	3.03 (1.68–5.46)	7	3.74 (1.39–10.07)	4	2.96 (0.69–10.01)	5	2.70 (0.92–7.99)
Ebstein anomaly	141	3	5.12 (1.00–16.34)	2	-	1	-	0	-	1	-
Septal defects											
Perimembranous VSD‖	1,110	6	1.10 (0.44–2.73)	11	4.13 (1.82–9.37)	5	6.58 (1.55–27.97)	5	2.83 (0.88–9.08)	3	2.63 (0.43–12.33)
Secundum ASD	2,307	17	1.45 (0.79–2.66)	23	2.35 (1.37–4.04)	10	3.25 (1.29–8.20)	7	2.41 (0.85–6.83)	10	3.22 (1.30–7.99)

Abbreviations: CHD, congenital heart defect; APVR, anomalous pulmonary venous return; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; VSD, ventricular septal defect; ASD, atrial septal defect.

*Medication classes are not mutually exclusive.

[†]Not presented in table are CHDs for which there were less than 3 exposed cases for every medication class: truncus arteriosus, DORV-TGA, conoventricular VSD, atrioventricular septal defect, aortic stenosis, tricuspid atresia, muscular VSD, single ventricle.

[≠]For CHD phenotypes with 3–4 exposed cases, calculated crude OR and exact CI; for 5+ exposed cases, adjusted for maternal race/ethnicity, BMI, age, early pregnancy smoking, and study site.

[§]Excludes CA cases and controls with EDD prior to 2002 (n=9801 controls).

[//]Only includes VSDs actively ascertained prior to EDD 2006 (n=5882 controls). VSDs collected for EDDs 2006–2011 in association with another defect are counted under the associated defect(s).

Table 4.

Association between early pregnancy antihypertensive medication use and selected CHDs, by study period.

	Overall 1997–2011 EDDs			1997–2003 EDDs*			2004–2011 EDDs		
Defect	**Unexp**	**Exp**	**OR (95% CI)†**	**Unexp**	**Exp**	**OR (95% CI)†**	**Unexp**	**Exp**	**OR (95% CI)†**
Controls	10,119	102		4,349	30		5,770	72	
Any CHD	9,359	164	1.59 (1.23–2.05)	4,322	66	1.92 (1.24–2.98)	5,037	98	1.47 (1.07–2.02)
Coarctation of the aorta	891	20	2.50 (1.52–4.11)	349	8	3.32 (1.47–7.50)	542	12	2.11 (1.12–4.00)
Pulmonary valve stenosis‡	1,191	33	2.19 (1.44–3.34)	470	10	2.39 (1.12–5.06)	721	23	2.25 (1.35–3.75)
Ebstein malformation	141	5	3.89 (1.51–10.06)	53	4	10.92 (2.70–32.60)	88	1	-
Secundum atrial septal defect	2,307	52	1.94 (1.36–2.79)	1,002	21	2.63 (1.45–4.76)	1,305	31	1.72 (1.08–2.73)
Perimembranous VSD§	1,110	19	1.90 (1.09–3.31)	766	10	1.61 (0.77–3.38)	344	9	2.65 (1.11–6.32)

Abbreviations: CHD, congenital heart defect; EDD, estimated date of delivery; VSD, ventricular septal defect.

*Numbers and estimates differ slightly from previous study[11] because of minor alterations to inclusion criteria and adjusted models.

†For CHD phenotypes with 3–4 exposed cases, calculated crude OR and exact CI; for 5+ exposed cases, adjusted for maternal race/ethnicity, BMI, age, early pregnancy smoking, and study site.

‡Excludes California cases and controls with EDD prior to 2002 (n=3930 unexposed and n=29 exposed controls during 1997–2003).

§Only includes VSDs actively ascertained prior to EDD 2006 (n=5882 controls).