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Maternal Antihypertensive Medication Use and Selected Birth Defects in the National Birth Defects Prevention Study

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Abstract

Background: There are limited data on the relationship between antihypertensive medication use in early pregnancy and risk of birth defects.

Methods: Using data from the National Birth Defects Prevention Study, we examined associations between specific antihypertensive medication classes and 28 non-cardiac birth defects. We analyzed self-reported data on 17,038 case and 11,477 control pregnancies with estimated delivery dates during 1997-2011. We used multivariable logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for maternal age, race/ethnicity, BMI, parity, pregestational diabetes, and study site, for associations between individual birth defects and antihypertensive medication use during the first trimester of pregnancy. We compared risk among women reporting early pregnancy antihypertensive medication use to normotensive women.

Results: Hypertensive women who reported early pregnancy antihypertensive medication use were more likely to be at least 35 years old, non-Hispanic Black, obese, multiparous, and to report pregestational diabetes than normotensive women. Compared to normotensive women, early pregnancy antihypertensive medication use was associated with increased risk of small intestinal atresia (adjusted OR 2.4, 95% CI 1.2-4.7) and anencephaly (adjusted OR 1.9, 95% CI 1.0-3.5). Risk of these defects was not specific to any particular medication class.

Conclusions: Maternal antihypertensive medication use was not associated with the majority of birth defects we analyzed, but was associated with an increased risk for some birth defects.

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Because we cannot entirely rule out confounding by the underlying hypertension and most ORs were based on small numbers, the increased risks observed should be interpreted with caution.

Keywords

birth defects; hypertension; antihypertensive; pregnancy; National Birth Defects Prevention Study

Introduction

Chronic hypertension affects approximately 2% of pregnant women in the United States (Bateman et al., 2012). There is clinical consensus that severe hypertension during pregnancy should be treated with antihypertensive medication. For mild-to-moderate hypertension during pregnancy, however, it remains unclear whether the risks of exposing the developing fetus to antihypertensive medications during early pregnancy outweigh the risks of untreated hypertension to the fetus and mother (Podymow & August, 2008). Prior National Birth Defects Prevention Study (NBDPS) analyses have reported increased risk of congenital heart defects (Caton et al., 2009; Fisher et al., 2017) and hypospadias (Caton et al., 2008; Van Zutphen et al., 2014) associated with antihypertensive medication use during pregnancy, supporting findings from analyses of data from other studies (Cooper et al., 2006; Czeizel, 1989; Kallen & Otterblad Olausson, 2003; Lennestal, Otterblad Olausson, & Kallen, 2009). Previous studies have also suggested associations with oral clefts (Puho, Szunyogh, Metneki, & Czeizel, 2007; van Gelder et al., 2015), esophageal atresia (Banhidy, Acs, Puho, & Czeizel, 2011a; Davis et al., 2011; van Gelder et al., 2015), and central nervous system (CNS) defects (Cooper et al., 2006; Medveczky, Puho, & Czeizel, 2004), although results for specific defects are inconsistent across studies. Other than the acknowledged fetopathic effects of angiotensin-converting enzyme (ACE) inhibitor use after the first trimester (Bullo, Tschumi, Bucher, Bianchetti, & Simonetti, 2012), there is little consensus on the relative risk or safety of other classes of antihypertensive medications during pregnancy. Animal models have raised concerns over the risk of limb defects associated with calcium channel blocker use (Danielsson, Reiland, Rundqvist, & Danielson, 1989; Ridings, Palmer, Davidson, & Baldwin, 1996), but these findings have not been corroborated by epidemiologic studies of humans (Magee et al., 1996; Sorensen, Czeizel, Rockenbauer, Steffensen, & Olsen, 2001; Weber-Schoendorfer et al., 2008).

Because antihypertensive medication use in early pregnancy is relatively rare, as are specific types of birth defects, investigators often analyze exposure to all antihypertensive medication classes combined. However, these medications operate through different mechanisms of action, which may affect fetal development differently. As the largest study of birth defects in the United States to date, NBDPS data can be used to assess risk of specific birth defects, with a large enough sample size to analyze antihypertensive medication class-specific effects. Our objective was to examine whether use of specific antihypertensive medication classes in early pregnancy is associated with risk of selected major non-cardiac structural birth defects.

Methods

The NBDPS was a multi-site, population-based, case-control study conducted to investigate risk factors for more than 30 major structural birth defects (Reefhuis et al., 2015). For our study, we analyzed birth defect case groups with at least 100 participants; we excluded congenital heart defects and hypospadias, as those case groups have been studied previously (Caton et al., 2009; Caton et al., 2008; Fisher et al., 2017; Van Zutphen et al., 2014). The NBDPS enrolled case and control women from 10 study sites located within Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Study eligibility began with pregnancies that ended on or after October 1, 1997 and concluded with pregnancies with estimated delivery dates (EDDs) on or before December 31, 2011. A woman 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 live births not affected by a birth defect randomly selected from birth certificates or hospital discharge records to represent the base population from which cases were selected in each study site. Medical record data were abstracted for all cases with an eligible defect within the study time period and geographic areas. Cases could be liveborn, stillborn after 20 weeks gestation, or induced abortions, with some variation across sites: New Jersey only ascertained live births; New York began ascertaining stillbirths and induced abortions in 2000; and Georgia began ascertaining induced abortions in 1999 and Massachusetts in 2011. Clinical geneticists reviewed abstracted data for all cases to determine eligibility; cases with known chromosomal abnormalities or single gene disorders were excluded. Eligible cases were classified as having either isolated, multiple, or complex birth defects (Rasmussen et al., 2003; Reefhuis et al., 2015). Briefly, a case with two or more major birth defects that are considered unrelated was classified as multiple; a case with a pattern of embryologically-related birth defects was classified as complex (e.g. Pentalogy of Cantrell or Omphalocele-Exstrophy-Imperforate anus-Spinal defects [OEIS] complex). With the exception of amniotic band sequence, we excluded complex cases from our study to reduce heterogeneity.

Hypertension exposure information was collected via maternal self-report during a computer-assisted telephone interview administered between 6 weeks and 24 months after her EDD. Trained interviewers asked respondents questions about 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 women with 1997–2005 EDDs and “high blood pressure, toxemia, pre-eclampsia or eclampsia” for women with 2006–2011 EDDs. Women reported the name, timing, and frequency of antihypertensive medication(s) used during the three months before pregnancy until delivery. Women with 2006–2011 EDDs also reported the type of hypertension (chronic, pregnancy-related, or both).

We defined a woman as exposed to antihypertensive medication if she reported having high blood pressure during the index pregnancy and reported using a medication in an antihypertensive class any time during the month before pregnancy through the third month of pregnancy ("first trimester"). We included the month prior to pregnancy as part of the first trimester to account for imperfect recall of the date of conception, as well as any lingering effects of medication used during the time immediately preceding conception. Women who reported hypertension during pregnancy, but no antihypertensive medication use, were defined as untreated hypertensives. We defined women who did not report high blood pressure and did not report any antihypertensive medication use during pregnancy as normotensive/unexposed. We excluded women who reported antihypertensive medication use only after the third pregnancy month, or who reported using an antihypertensive medication class but did not report high blood pressure, or who were missing interview responses to the hypertension questions (n=605 cases, 352 controls).

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 (ACE inhibitors, angiotensin receptor blockers), calcium channel blockers, diuretics, and direct vasodilators.

We conducted multivariable logistic regression analysis to estimate the risk of birth defects associated with early pregnancy antihypertensive medication use, overall and by medication class, compared to that of normotensive women. Because the etiology of isolated birth defects may differ from that of multiple co-occurring defects, we did a sub-analysis of isolated cases. As another sub-analysis, to assess potential confounding by the underlying hypertension, we restricted our sample to women who were asked about the type of hypertension and compared the risk of birth defects associated with untreated chronic hypertension to that of normotensive pregnancies. For defect groups with at least five exposed cases, we calculated adjusted odds ratios (aORs) and 95% confidence intervals (CIs), adjusted for a set of covariates selected *a priori,* based on existing knowledge and literature review. Our final adjusted model controlled for maternal age (<20 years, 20-34 years, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), pre-pregnancy body mass index (BMI) (underweight: <18.5, normal: 18.5-24, overweight: 25-29, obese: ≥30), parity (primiparous vs. multiparous), preexisting type 1 or type 2 diabetes, and study site. For case groups with 3-4 exposed cases, we calculated crude odds ratios (cORs) and Fisher's exact CIs. We used SAS 9.4 for all statistical analyses.

Results

After exclusions, we analyzed data on 17,038 birth defect cases and 11,477 controls. Overall, 1.4% of cases (n=241) and 1.1% of controls (n=124) reported first trimester antihypertensive medication use, and 8.0% of cases (n=1,359) and 7.9% of controls (n=906) reported untreated hypertension during pregnancy. Based on the subset of women who were asked about the type of hypertension (n=4,822 controls, 7,267 cases), the majority of first trimester antihypertensive users (n=78, or 78.0% of cases; n=44, or 73.3% of controls) reported only chronic hypertension, whereas only 8.7% of untreated hypertensive cases

(n=51) and 7.2% of untreated hypertensive controls (n=25) reported chronic hypertension (Figure 1). Among controls, women who reported first trimester antihypertensive use were more likely to be at least 35 years old, non-Hispanic Black, obese, to have had at least one previous birth, to have preexisting diabetes, to report taking a folic acid-containing supplement during early pregnancy than normotensive women, and to report antidiabetic, antidepressant, and antilipemic medication use (Table 1). Characteristics among our subset of untreated chronic hypertensive controls (n=25) were similar to treated controls (data not shown). Excluded controls (n=352) were more likely to be non-Hispanic Black or Hispanic, but were otherwise similar to included controls (data not shown). Among first-trimester antihypertensive users, the most commonly reported antihypertensive classes were centrally-acting antiadrenergics (37% controls, 33% cases) and β-blockers (37% cases, 40% controls) (data not shown).

Compared to normotensive women, women exposed to first trimester antihypertensive medications had increased risk of small intestinal atresia (aOR 2.4, 95% CI 1.2-4.7) and anencephaly (aOR 1.2, 95% CI 1.0-3.5) (Table 2). We also observed a positive crude association between antihypertensive use and cloacal exstrophy, based on 4 exposed cases (cOR 3.8, 95% CI 1.0-10.4). We observed less stable, but greater than 50% increased risk for anophthalmia, glaucoma, biliary atresia, and bilateral renal agenesis. Our analysis restricted to isolated cases largely mirrored these results, with the exception of cloacal exstrophy and biliary atresia, which did not have enough exposed isolated cases to calculate ORs (n=2 exposed cases each).

We observed elevated ORs for several antihypertensive medication classes and anencephaly: β-blockers (aOR 2.6, 95% CI 1.0-6.4), diuretics (cOR 4.3, 95% CI 1.1-13.4), and renin-angiotensin system blockers (cOR 3.8, 95% CI 0.9-12.0) (Table 3). One other CNS defect, hydrocephaly, was positively associated with diuretic use (cOR 6.0, 95% CI 1.5-18.7), and another, encephalocele, was positively associated with centrally-acting antiadrenergic use (aOR 4.1, 95% CI 1.5-11.2). We also observed associations between small intestinal atresia and both β-blockers (aOR 2.9, 95% CI 1.1-7.5) and calcium channel blockers (aOR 11.2, 95% CI 3.7-34.2), the only two classes for which we calculated estimates for this defect. Finally, we found notably elevated crude associations between cloacal exstrophy and β-blockers (cOR 7.1, 1.4-22.7) and between sacral agenesis and renin-angiotensin system blockers (cOR 21.2, 95% CI 3.9-74.7), but both estimates were based on only 3 exposed cases and had wide confidence intervals. For the remaining birth defects analyzed, ORs were imprecise, but several were elevated more than two-fold.

Our sub-analysis of women who reported untreated chronic hypertension was limited by small numbers (Table 4); we could not calculate ORs for 24 of the case groups included in our main analysis. We calculated crude ORs for 7 defects and an adjusted OR for 1: spina bifida (n=6 exposed cases). Confidence intervals were wide, but all ORs for the association between untreated chronic hypertension and birth defects were similar or higher than those observed for the association between antihypertensive medication use and the same defects. We observed more than 50% increased risk of spina bifida, cataracts, cleft clip, small intestinal atresia, longitudinal limb deficiency, and diaphragmatic hernia, compared to normotensive pregnancies.

Discussion

We observed that first trimester antihypertensive use was not associated with an increased risk of most of the 28 non-cardiac birth defects analyzed. However even in our large study, antihypertensive medication use was rare, limiting our ability to detect moderate effects. We observed increased risk of small intestinal atresia and anencephaly, which were not clearly confined to any particular class of antihypertensive medications. Prior studies have also indicated possible associations between maternal hypertension and/or antihypertensive use and esophageal atresia (Puho et al., 2007; van Gelder et al., 2015) and oral clefts (Banhidy et al., 2011a; Davis et al., 2011; van Gelder et al., 2015); our data do not support those findings.

The more than two-fold increased risk of small intestinal atresia associated with any antihypertensive medication use was driven by calcium channel blocker and β-blocker users. One registry-based study from Hungary reported increased risk of intestinal atresia/stenosis associated with chronic hypertension during pregnancy, regardless of treatment status (OR 2.3, 95% CI 0.9-6.0) (Banhidy et al., 2011a), but did not analyze specific medications nor specific types of intestinal atresia/stenosis. Another study using US Medicaid data reported no associations between either treated or untreated chronic hypertension and unspecified gastrointestinal malformations (Bateman et al., 2015). Studies focusing specifically on the effects of calcium channel blocker or β-blocker use in pregnancy did not have enough exposed intestinal atresia cases to estimate odds ratios (Davis et al., 2011; Sorensen et al., 2001). We did not observe strong evidence for associations between antihypertensive use and any gastrointestinal defects other than small intestinal atresia, although our analysis was limited by small numbers. We observed elevated crude odds ratios for duodenal and biliary atresia (1.7 and 2.0, respectively), but our sample did not have enough power to detect statistically significant ORs of less than 2.5. Our findings for cloacal exstrophy are unadjusted and based on less than five exposed cases so should be interpreted cautiously. Cloacal exstrophy is a rare defect and to our knowledge this potential association is not reported elsewhere in the literature.

In addition to our observed elevated ORs for anencephaly, other CNS defects were associated with specific antihypertensive classes, notably encephalocele and hydrocephaly. There is limited support for these findings from some prior studies (Cooper et al., 2006; Li, Yang, Andrade, Tavares, & Ferber, 2011; van Gelder et al., 2015), but not all (Bateman et al., 2015; Bateman et al., 2017; Bergman et al., 2018). None of these prior studies presented estimates for specific CNS defects, and only two included non-liveborn cases. Our most compelling results among the CNS defects analyzed were for anencephaly; anencephaly cases, in particular, are likely to be under-ascertained if stillbirths and terminations are excluded (Johnson et al., 2012). One widely-publicized study reported an association between CNS defects and first trimester ACE inhibitor use, specifically (Cooper et al., 2006), but a subsequent study with more robust control for confounders and more exposed cases reported no association (Bateman et al., 2017). Our findings of increased risk associated with centrally-acting antiadrenergics (encephalocele), β-blockers (anencephaly), renin-angiotensin system blockers (anencephaly), and diuretics (anencephaly and hydrocephaly) support those of others who assert that early pregnancy antihypertensive

use may increase risk of CNS defects, but that this risk is not limited to ACE inhibitors (Li et al., 2011; van Gelder et al., 2015). However, several of our class-specific estimates were crude and may be confounded by other factors.

We estimated a notably high crude odds ratio (cOR 21.2, 95% CI 3.9-74.7) for the association between renin-angiotensin system blocker use and sacral agenesis. We caution against over-interpreting this estimate, however, because it was based on only three exposed cases, all of whom also reported pre-gestational diabetes. Type 2 diabetes is known to be strongly associated with sacral agenesis (Correa et al., 2008), which is most likely confounding our observed association with antihypertensive use.

Some have hypothesized that certain birth defects, including small intestinal and renal atresias have vascular origins (Koga, Hayashida, Ikeda, Inokuchi, & Hashimoto, 1975; Louw & Barnard, 1955). Antihypertensive medications are, by definition, vasoactive, which may explain the associations we observed with these particular defects. However, we did not observe any evidence for an association between antihypertensive medication and other defects thought to result from vascular disruption: transverse limb deficiencies and gastroschisis (Sadler & Rasmussen, 2010). Additionally, the vascular disruption hypothesis traditionally focuses on agents that are vasoconstrictive or events that involve mechanical blockage of blood supply to the affected organ (Koga et al., 1975; Webster & Brown-Woodman, 1990; Werler, Sheehan, & Mitchell, 2003). Some antihypertensive medication classes can have vasoconstrictive effects (selective β-blockers and diuretics), but others are vasodilating (non-selective β-blockers, centrally-acting antiadrenergic agents, calcium channel blockers, ACE inhibitors, direct vasodilators) (Brunner, Nussberger, & Waeber, 1985; Easterling, 2014). We observed positive associations for the same defects across differently-acting medication classes, further calling into question this biologic mechanism.

Antihypertensive medications, regardless of mechanism, share the end result of reducing blood pressure. Combined with the lowering of maternal blood pressure that naturally occurs at the beginning of pregnancy, unintentional hypotension may play a role in impairing fetal development. However this theory is not supported by limited available evidence (Banhidy, Acs, Puho, & Czeizel, 2011b).

Another hypothesis is that reduced uteroplacental perfusion resulting from the underlying hypertensive condition could explain the increased risk of birth defects that we observed across several different medication classes. We attempted to account for this by conducting a sub-analysis of birth defect risk among untreated chronic hypertensive women compared to normotensive women. In general, the defects for which we observed an association with untreated hypertension were not the same as those for which we observed an association with antihypertensive medication. Most of the defects for which we observed elevated point estimates among untreated hypertensive women (spina bifida, cataracts, longitudinal limb deficiency, diaphragmatic hernia) had null associations with antihypertensive medication use, suggesting that poorly controlled hypertension may be a risk factor for these birth defects and treatment may in fact have a protective effect. We were unable to calculate ORs for risk of untreated hypertension for several birth defects for which we observed elevated ORs for risk of treated hypertension. We did not calculate an OR for anencephaly,

as there were only 2 cases among untreated chronic hypertensive women. The OR for small intestinal atresia (cOR 2.9, 95% CI 0.6-9.8) was imprecise but similar to what we observed for treated women overall (AOR 2.4, 95% CI 1.2-4.7) and for β-blocker users (AOR 2.9, 95% CI 1.1-7.5), but lower than our estimate for calcium channel blocker users (AOR 11.2, 95% CI 3.7-34.2). These results indicate that the underlying hypertensive disease may be driving some, but not necessarily all, of the risk among antihypertensive medication users. However, it is also possible that women who require antihypertensive treatment have more severe disease than untreated hypertensive women; we were unable to control for hypertension severity in our analysis. We only have information on the type of hypertension for a subset of our study population, and no information on clinical blood pressure measurements, limiting our ability to assess confounding by indication.

Despite being the largest population-based case-control study of birth defects in the United States, reported antihypertensive medication use is rare in the NBDPS population, as are individual birth defects. At $\beta=0.2$ and $\alpha=0.05$, minimum detectable ORs for our main analyses of early pregnancy antihypertensive medication use and each birth defect (Table 2) range from 1.6 to 2.5. We observed non-significant aORs that were at least 50% increased, but lower than the minimum detectable ORs, for four case groups (Dandy-Walker malformation, anophthalmia/microphthalmia, glaucoma, and anotia/microtia). These may represent true associations that our study was under-powered to differentiate from null findings; however to our knowledge there is no evidence from other studies that these particular birth defects are associated with maternal antihypertensive use. The range of minimum detectable ORs for our class-specific analyses (Table 3) is 2.1 to 2.9, making it difficult to interpret the number of non-significantly elevated estimates that did not meet this threshold.

As with all case-control studies, it is possible that case women were more likely to recall details about their pregnancy exposures than control women. However, antihypertensive medication is generally a long-term, daily treatment for a chronic condition, reducing the likelihood that a woman, regardless of case/control status, would not remember it. Furthermore, trained interviewers had a list of common antihypertensive medications that they could read from to assist with recall, if necessary. Finally, some of our results might be due to chance. We estimated over 100 comparisons and numbers were small, limiting precision of ORs.

Despite the limitations, our study also has several strengths. The NBDPS is the largest study of birth defects in the US, collecting detailed information on antihypertensive use, as well as potential confounding exposures. NBDPS employs a robust case classification protocol, enabling us to study specific birth defect phenotypes. With study sites in ten geographic locations throughout the US, our population is culturally and demographically diverse. Our study raises concerns about the association between antihypertensive medication and two particular birth defects: small intestinal atresia and anencephaly. These associations have not been reported in previous studies, which may be because they are chance findings, or possibly because other studies have been unable to analyze these specific defects. Nevertheless, it is important to note that we did not observe stable and strong associations between antihypertensive medication use in early pregnancy and most of the birth defects we

studied. Our findings for small intestinal atresia and central nervous system defects warrant further investigation. We were not able to evaluate safety of class-specific treatments, but overall, antihypertensive medication use in early pregnancy was not strongly associated with most birth defects analyzed.

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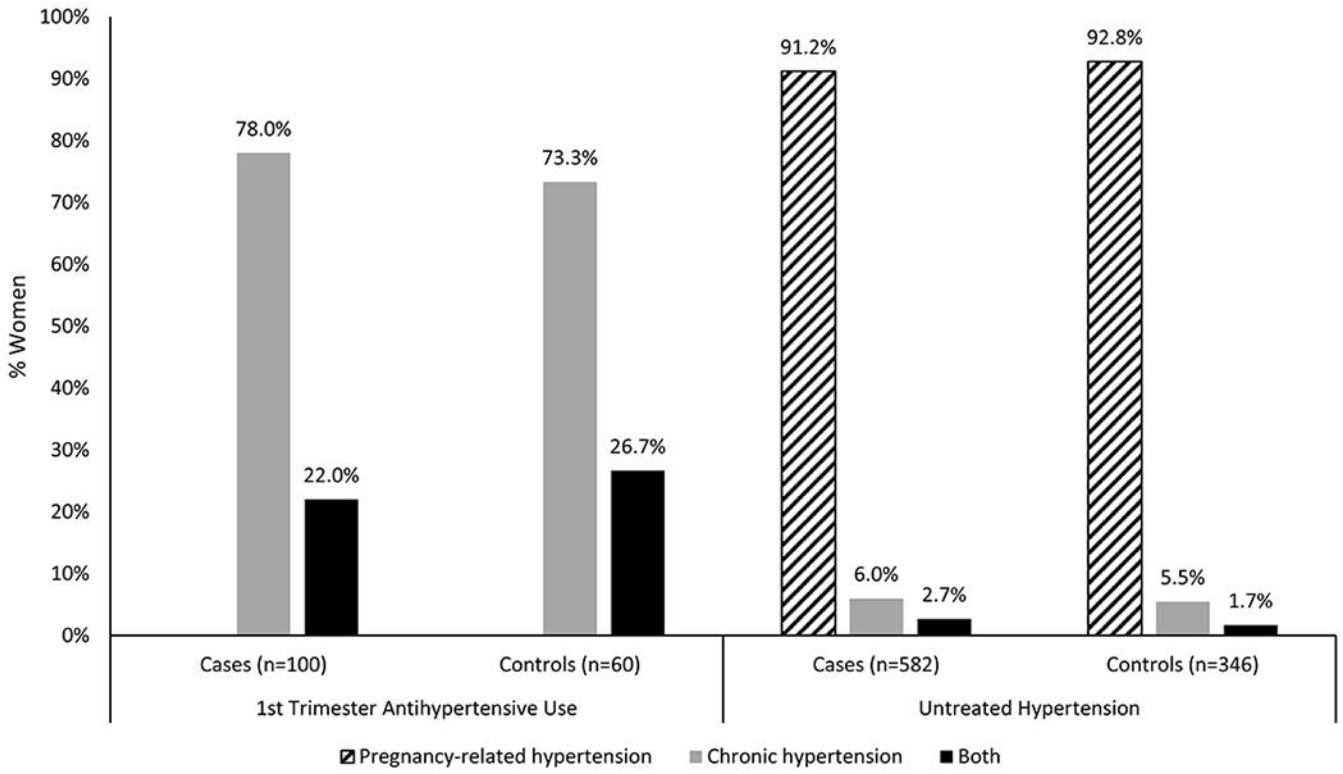

Figure 1.

Reported type of hypertension among hypertensive pregnancies, by case/control and antihypertensive treatment status, NBDPS 2006-2011.

Table 1.

Maternal characteristics of included controls, by antihypertensive medication exposure status, NBDPS 1997-2011.

	Normotensive (n=10,447)[a]	1st Trimester Antihypertensive Use (n=124)[a]	
Maternal Characteristic	**n (%)**	**n (%)**	***p*-value**
Age at delivery			<0.001
<20 years	1014 (9.7)	1 (0.8)	
20-34 years	7996 (76.5)	76 (61.3)	
≥35 years	1437 (13.8)	47 (37.9)	
Race/Ethnicity			<0.001
Non-Hispanic white	6054 (58.0)	60 (48.4)	
Non-Hispanic black	1096 (10.5)	37 (29.8)	
Hispanic	2593 (24.8)	18 (14.5)	
Other	698 (6.7)	9 (7.26)	
Pre-pregnancy BMI			<0.001
Underweight	550 (5.5)	1 (0.8)	
Normal	5532 (55.3)	25 (20.2)	
Overweight	2238 (22.4)	23 (18.6)	
Obese	1681 (16.8)	75 (60.5)	
Parity ≥1	6419 (61.4)	92 (74.2)	0.004
Pre-gestational diabetes	54 (0.6)	13 (12.4)	<0.001
Early pregnancy[b] folic acid supplement use	5485 (52.5)	73 (59.4)	<0.001
First trimester cigarette smoking	1844 (17.8)	21 (17.4)	0.90
First trimester binge alcohol consumption	1290 (16.6)	11 (12.1)	0.25
First trimester cocaine use	37 (0.7)	0 (0)	0.51
Other first trimester medication use			
Antidiabetic medication use	28 (0.3)	8 (6.5)	<0.001
Antidepressant medication use	409 (3.9)	14 (11.4)	<0.001
Antilipemic medication use	4 (0.04)	1 (0.8)	<0.001
Any prenatal care	10,334 (98.9)	124 (100)	0.72
Education level			0.17
<High school	1726 (16.7)	14 (11.6)	
HS diploma	2452 (23.7)	23 (19.0)	
Some college	2699 (26.1)	37 (30.6)	
Bachelor's degree or higher	3452 (33.4)	47 (38.84)	
Household income			0.30
<$30k	4328 (45.5)	49 (41.5)	
$30-49k	1642 (17.3)	17 (14.4)	
≥$50k	3537 (37.2)	52 (44.1)	

[a] Totals for each characteristic may be less due to item non-response.

[b] Any use during the month before and after conception.

Table 2.

Association between first trimester antihypertensive medication use and birth defects compared to normotensive pregnancies, among cases with isolated and multiple defects and among isolated cases only, NBDPS, 1997-2011.

	All Non-Complex Cases			Isolated Cases Only		
Defect	**Normotensive**	**Exposed**	**OR (95% CI)[a]**	**Normotensive**	**Exposed**	**OR (95% CI)[a]**
Controls	10447	124	1.0 (ref)	10447	124	1.0 (ref)
Cases	15438	241	-	12661	180	
Amniotic band sequence and limb body wall complex [ABS-LBWC]	307	4	1.1 (0.3-2.9)	261	2	-
ABS-LBWC: Limb anomalies only	196	3	1.3 (0.3-3.9)	171	1	-
Central nervous system defects						
Anencephaly	606	15	1.9 (1.0-3.5)	540	15	2.3 (1.2-4.2)
Spina bifida	1157	13	0.7 (0.4-1.4)	1020	12	0.8 (0.4-1.6)
Encephalocele	201	5	1.4 (0.5-3.8)	150	5	1.6 (0.6-4.5)
Hydrocephaly	436	8	0.9 (0.4-2.2)	294	3	0.9 (0.2-2.6)
Dandy-Walker malformation	153	5	1.5 (0.5-4.5)	96	1	-
Holoprosencephaly	156	1	-	111	0	-
Eye and ear defects						
Cataracts	314	1	-	279	1	-
Anophthalmia/microphthalmia	203	5	1.8 (0.7-4.8)	120	3	2.1 (0.4-6.5)
Glaucoma/anterior chamber defects	151	5	2.0 (0.7-5.8)	124	4	2.5 (0.7-6.8)
Anotia/microtia	624	11	1.5 (0.7-3.0)	432	7	2.2 (1.0-5.1)
Orofacial defects						
Choanal atresia	148	2	-	81	1	-
Cleft palate only[b]	1439	25	1.1 (0.7-1.9)	1157	17	1.1 (0.6-1.9)
Cleft lip with cleft palate[b]	1796	21	0.9 (0.5-1.5)	1522	19	1.0 (0.6-1.7)
Cleft lip only[b]	970	14	1.2 (0.6-2.3)	903	13	1.3 (0.7-2.5)
Gastrointestinal defects						
Esophageal atresia	657	10	0.9 (0.4-1.9)	272	4	1.2 (0.3-3.3)
Small intestinal atresia/stenosis	420	13	2.4 (1.2-4.7)	358	13	2.6 (1.3-5.1)
Duodenal atresia/stenosis	200	4	1.7 (0.5-4.5)	124	2	-

	All Non-Complex Cases			Isolated Cases Only		
Defect	**Normotensive**	**Exposed**	**OR (95% CI)[a]**	**Normotensive**	**Exposed**	**OR (95% CI)[a]**
Anorectal atresia/stenosis	779	16	1.0 (0.5-1.8)	414	6	0.7 (0.3-1.9)
High anorectal atresia/stenosis	178	1	-	74	0	-
Low anorectal atresia/stenosis	415	8	1.1 (0.5-2.5)	278	5	1.0 (0.4-2.9)
Cloacal exstrophy	88	4	3.8 (1.0-10.4)	53	2	-
Biliary atresia	173	4	2.0 (0.5-5.2)	148	2	-
Genitourinary defects						
Bilateral renal agenesis/hypoplasia	163	4	2.1 (0.6-5.5)	117	4	2.9 (0.8-7.8)
Musculoskeletal defects						
Longitudinal/intercalary limb deficiency	477	8	0.7 (0.3-1.7)	277	4	1.2 (0.3-3.2)
Transverse limb deficiency	638	9	1.2 (0.6-2.6)	538	5	0.9 (0.4-2.3)
Craniosynostosis	1405	18	1.0 (0.5-1.8)	1273	17	1.0 (0.6-1.9)
Diaphragmatic hernia	764	10	0.9 (0.4-1.8)	592	7	0.9 (0.4-2.2)
Gastroschisis	1324	6	1.1 (0.4-2.8)	1199	6	1.2 (0.5-3.1)
Omphalocele	374	6	0.4 (0.1-1.4)	228	5	0.9 (0.3-3.0)
Sacral agenesis	82	5	0.9 (0.2-3.2)	10	0	-

[a] For case groups with at least 5 exposed cases, estimates are adjusted for maternal age, race/ethnicity, BMI, parity, pregestational diabetes, and study site. For case groups with 3-4 exposed cases, we calculated crude ORs with exact confidence intervals.

[b] For analyses of oral clefts, n=10,330 normotensive controls, 124 antihypertensive-exposed controls

Table 3.

Association between first trimester antihypertensive medication use and birth defects, by antihypertensive medication class, compared to normotensive pregnancies, NBDPS 1997-2011. Medication class categories are not mutually exclusive, so women who report multiple medications may be counted in more than one column.

		Centrally-Acting Antiadrenergics		Beta Blockers		Renin-Angiotensin System Blockers		Calcium Channel Blockers		Diuretics	
Defect[a]	**Unexp**	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]
Controls	10,447	46	1.0 (ref)	50	1.0 (ref)	18	1.0 (ref)	14	1.0 (ref)	16	1.0 (ref)
All Cases	15,438	78		90		44		27		39	
ABS-LBWC	307	3	2.2 (0.4-7.0)	1	-	0	-	0	-	0	-
Central nervous system defects											
Anencephaly	606	5	1.3 (0.5-3.8)	6	2.6 (1.0-6.4)	4	3.8 (0.9-11.7)	2	-	4	4.3 (1.1-13.4)
Spina bifida	1,157	2	-	7	1.0 (0.4-2.6)	1	-	1	-	3	1.7 (0.3-5.9)
Encephalocele	201	5	4.1 (1.5-11.2)	1	-	0	-	0	-	0	-
Hydrocephaly	436	2	-	3	1.4 (0.3-4.5)	1	-	0	-	4	6.0 (1.5-18.7)
Eye and ear defects											
Anotia/microtia	624	4	1.5 (0.4-4.0)	4	1.3 (0.4-3.7)	2	-	1	-	2	-
Orofacial defects											
Cleft palate only[c]	1,439	8	0.9 (0.4-2.2)	7	0.9 (0.4-2.1)	6	1.4 (0.5-4.3)	2	-	6	1.9 (0.6-6.1)
Cleft lip with cleft palate[c]	1,796	9	0.8 (0.3-1.9)	8	1.1 (0.5-2.3)	5	0.9 (0.3-3.0)	0	-	4	1.4 (0.4-4.5)
Cleft lip only[c]	970	4	0.9 (0.2-2.5)	7	1.5 (0.6-3.6)	3	1.8 (0.3-6.1)	4	3.0 (0.7-9.7)	2	-
Gastrointestinal defects											
Esophageal atresia	657	2	-	4	1.3 (0.3-3.5)	3	2.7 (0.5-9.1)	1	-	0	-
Small intestinal atresia/stenosis	420	2	-	6	2.9 (1.1-7.5)	2	-	7	11.2 (3.7-34.2)	0	-
Anorectal atresia/stenosis	779	4	1.2 (0.3-3.2)	5	0.8 (0.3-2.5)	3	2.2 (0.4-7.7)	1	-	1	-
Low anorectal atresia/stenosis	415	3	1.6 (0.3-5.1)	3	1.5 (0.3-4.7)	1	-	1	-	0	-
Cloacal exstrophy	88	1	-	3	7.1 (1.4-22.7)	0	-	0	-	2	-
Musculoskeletal defects											
Longitudinal/intercalary limb deficiency	477	3	1.4 (0.3-4.5)	3	1.3 (0.3-4.1)	2	-	0	-	2	-
Transverse limb deficiency	638	4	1.4 (0.4-3.9)	2	-	2	-	1	-	1	-

		Centrally-Acting Antiadrenergics		Beta Blockers		Renin-Angiotensin System Blockers		Calcium Channel Blockers		Diuretics	
Defect[a]	**Unexp**	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]	**Exp**	**OR (95% CI)**[b]
Craniosynostosis	1,405	8	0.8 (0.3-2.3)	7	1.0 (0.4-2.5)	2	-	0	-	0	-
Diaphragmatic hernia	764	3	0.9 (0.2-2.8)	4	1.1 (0.3-3.0)	1	-	2	-	0	-
Gastroschisis	1,324	2	-	3	0.5 (0.1-1.5)	3	1.3 (0.3-4.5)	0	-	2	-
Sacral agenesis	82	1	-	1	-	3	21.2 (3.9-74.7)	0	-	1	-

Abbreviations: Unexp, unexposed; Exp, exposed; ABS-LBWC, amniotic band sequence-limb body wall complex.

[a]Several case groups included in Table 2 had less than 3 exposed cases for each medication class, so were excluded from this table: ABS-LBWC with only limb anomalies, Dandy-Walker malformation, holoprosencephaly, cataracts, anopthalmos/micropthalmos, glaucoma/anterior chamber defects, choanal atresia, duodenal atresia/stenosis, high anorectal atresia/stenosis, biliary atresia, bilateral renal agenesis/hypoplasia, omphalocele. There were 8 cases exposed to vasodilators, but not more than 2 in any one case group, so that exposure category is also excluded from this table.

[b]For case groups with at least 5 exposed cases, estimates are adjusted for maternal age, race/ethnicity, BMI, parity, pregestational diabetes, and study site. For case groups with 3-4 exposed cases, we calculated crude ORs with exact confidence intervals.

[c]For analyses of oral clefts, n=10,330 normotensive controls, 124 antihypertensive-exposed controls

Table 4.

Association of untreated chronic maternal hypertension and birth defects, compared to normotensive pregnancies, NBDPS 2006-2011.

Defect[a]	Normotensive	Untreated	OR (95% CI)[b]
Controls	4404	25	1.0 (ref)
Cases	6562	51	-
Amniotic band sequence and limb body wall complex	115	1	-
Central nervous system defects			
Anencephaly	272	2	-
Spina bifida	489	6	2.5 (1.0-6.5)
Hydrocephaly	170	1	-
Eye and ear defects			
Cataracts	150	4	4.7 (1.2-13.8)
Anotia/microtia	252	2	-
Orofacial defects			
Cleft palate only	564	4	1.3 (0.3-3.6)
Cleft lip with cleft palate	745	4	1.0 (0.2-2.8)
Cleft lip only	418	4	1.7 (0.4-4.9)
Gastrointestinal defects			
Esophageal atresia	264	2	-
Small intestinal atresia/stenosis	180	3	2.9 (0.6-9.8)
Duodenal atresia/stenosis	99	1	-
Anorectal atresia/stenosis	298	2	-
High anorectal atresia/stenosis	72	1	-
Biliary atresia	77	2	-
Musculoskeletal defects			
Longitudinal or intercalary limb deficiency	181	3	2.9 (0.6-9.7)
Transverse limb deficiency	271	2	-
Craniosynostosis	675	2	-
Diaphragmatic hernia	313	3	1.7 (0.3-5.6)
Gastroschisis	633	1	-
Omphalocele	137	2	-

[a]The following defect groups were included in the main analysis but were dropped from this table because there were 0 exposed cases: Amniotic band sequence and limb body wall complex with only limb anomalies, encephalocele, Dandy-Walker malformation, holoprosencephaly, anophthalmia/microphthalmia, glaucoma/anterior chamber defects, choanal atresia, low anorectal atresia, cloacal exstrophy, bilateral renal agenesis/hypoplasia, sacral agenesis.

[b]For case groups with at least 5 exposed cases, estimates are adjusted for maternal age, race/ethnicity, BMI, parity, pregestational diabetes, and study site. For case groups with 3-4 exposed cases, we calculated crude ORs with exact confidence intervals.