

Antihypertensive Medication Use During Pregnancy and the Risk of Cardiovascular Malformations

Alissa R. Caton, Erin M. Bell, Charlotte M. Druschel, Martha M. Werler, Angela E. Lin, Marilyn L. Browne, Louise-Anne McNutt, Paul A. Romitti, Allen A. Mitchell, Richard S. Olney, Adolfo Correa; for the National Birth Defects Prevention Study

Abstract—We used data from the National Birth Defects Prevention Study, a population-based, case-control study, to examine whether previously reported associations between antihypertensive medications and cardiovascular malformations could be confirmed and to explore whether new associations might be identified. Cases (n=5021) were ascertained through birth defects surveillance systems from 1997 through 2003 in 10 US states. Controls (n=4796) were live births without birth defects selected randomly from birth certificates or hospital discharge listings in the same geographic regions. Logistic regression was used to examine the relationship between antihypertensive medication treatment and the occurrence of cardiovascular malformations while controlling for confounding variables. First-trimester treatment with antihypertensive medication was associated with pulmonary valve stenosis (odds ratio [OR]: 2.6; 95% CI: 1.3 to 5.4), Ebstein malformation (crude OR: 11.4; exact 95% CI: 2.8 to 34.1), coarctation of the aorta (OR: 3.0; 95% CI: 1.3 to 6.6), and secundum atrial septal defects (OR: 2.4; 95% CI: 1.3 to 4.4). Treatment initiated after the first trimester was associated with pulmonary valve stenosis (OR: 2.4; 95% CI: 1.1 to 5.4), perimembranous ventricular septal defects (OR: 2.3; 95% CI: 1.2 to 4.6), and secundum atrial septal defects (OR: 2.4; 95% CI: 1.3 to 4.4). Untreated hypertension was associated with Ebstein malformation (OR: 2.1; 95% CI: 1.0 to 4.3) and secundum atrial septal defects (OR: 1.3; 95% CI: 1.0 to 1.6). Antihypertensive medication use and/or the underlying hypertension might increase the risk of having an infant with specific left and right obstructive and septal defects. Additional studies with adequate power will be needed to confirm these findings. (*Hypertension*. 2009;54:63-70.)

Key Words: hypertension ■ pregnancy ■ antihypertensive agents ■ congenital malformations ■ cardiovascular malformations

Hypertension occurs in 5% to 10% of pregnancies,¹⁻⁶ yet information on the safety of antihypertensive medication use during pregnancy is limited. For severe hypertension, antihypertensive medication is used to prevent serious maternal and fetal complications; however, there is no consensus on when to treat mild-to-moderate hypertension. Although treatment with medication might benefit the mother, it carries potential risks to the fetus from both impaired uteroplacental perfusion and fetal exposure to the medications. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, 2 classes with similar mechanisms of action, are contraindicated during the second and third trimesters because of a well-known fetopathy.¹⁻¹¹ The β -blocker atenolol has been associated with intrauterine growth retardation.^{1-6,12-14}

One concern is that hypertension or iatrogenic hypotension might cause cardiovascular malformations (CVMs) by alter-

ing perfusion in the placenta and/or fetus.¹⁵⁻¹⁹ In rats, abnormal cardiac development has resulted from exposures to calcium channel blockers, angiotensin II receptor blockers, and centrally acting antiadrenergic agents.^{7,18-20} In humans, findings regarding hypertension and its treatments in relation to the risk of CVMs have been inconsistent.²¹⁻²⁶ A recent study of first-trimester ACE inhibitor use in the Tennessee Medicaid population reported an increased risk of CVMs.²¹ Because risks were not increased among women treated with other classes of antihypertensive medications, the authors suggested that the observed association was attributable to the medication and not to the underlying hypertension. In contrast, a study from the Swedish Medical Birth Register subsequently showed a significant association between maternal use of antihypertensive medications and CVMs that was not specific to ACE inhibitors.²²

Received January 12, 2009; first decision January 28, 2009; revision accepted April 14, 2009.

From the Department of Epidemiology and Biostatistics (A.R.C., E.M.B., C.M.D., M.L.B., L.-A.M.), School of Public Health, University at Albany, Rensselaer, NY; Congenital Malformations Registry (A.R.C., C.M.D., M.L.B.), New York State Department of Health, Troy; Slone Epidemiology Center (M.M.W., A.A.M.), Boston University, Mass; Genetics Unit (A.E.L.), MassGeneral Hospital for Children, Boston; Department of Epidemiology (P.A.R.), College of Public Health, University of Iowa, Iowa City; and the National Center on Birth Defects and Developmental Disabilities (R.S.O., A.C.), Centers for Disease Control and Prevention, Atlanta, Ga.

Correspondence to Alissa R. Caton, New York State Department of Health, Bureau of Environmental and Occupational Epidemiology, 547 River St, Room 200, Troy, NY 12180-2216. E-mail arc05@health.state.ny.us

© 2009 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.109.129098

We used data from the National Birth Defects Prevention Study (NBDPS) to examine whether previously reported associations between antihypertensive medications and CVMs could be confirmed and to explore whether new associations might be identified.

Methods

National Birth Defects Prevention Study

The NBDPS is an ongoing, multisite, population-based, case-control study investigating genetic and environmental risk factors of >30 major structural birth defects.^{27–29} This analysis includes cases of CVMs and controls born to mothers with estimated dates of delivery from October 1997 through December 2003 from 10 participating states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Case infants were identified from the population-based birth defects surveillance systems of the participating centers and included live births, fetal deaths occurring after 20 weeks, and elective pregnancy terminations. Control infants were live births without birth defects randomly selected from birth certificates or hospital discharge listings in the same geographic areas as the cases.

Standard procedures, as described by Yoon et al,²⁹ were used for contacting and interviewing mothers of infants within 24 months after the estimated dates of delivery. Information was collected using a computer-assisted telephone interview in either English or Spanish. The interview included questions on maternal medical and pregnancy history, medication use, family demographics, nutrition, and behaviors. Among eligible mothers, 71% of cases and 69% of controls participated. Compared with nonparticipants, interviewed mothers were more likely to be white non-Hispanic, older, to have attained more than a high school education, and to have begun prenatal care in the first trimester. Each center obtained institutional review board approval for the NBDPS and informed consent from each mother, and the study adhered to the principles of the Declaration of Helsinki.

Clinical Review and Case Classification

Clinical geneticists reviewed abstractions of medical charts of CVM cases identified by centers to ensure that each infant fulfilled the study case definition and diagnostic criteria.²⁸ The NBDPS does not include infants with isolated patent ductus arteriosus, patent foramen ovale, certain rare CVMs, or recognized single gene disorders or chromosome abnormalities. An eligible CVM required diagnosis by high-level prenatal ultrasonography, echocardiography, catheterization, surgery, or autopsy. The defects eligible for the NBDPS, in order of embryological development, were heterotaxy/situs inversus, single ventricle, conotruncal defects, atrioventricular septal defects, right ventricular outflow tract obstructions (RVOTOs), left ventricular outflow tract obstructions (LVOTOs), septal defects, and anomalous pulmonary venous return.²³ Details of the NBDPS CVM classification methods are described by Botto et al.³⁰

Exposure Assessment

The interview asked about the diagnosis, timing, and treatment of high blood pressure but did not identify type of hypertension (eg, chronic or preeclampsia). Information was collected on all use of antihypertensive medications between 3 months preconception through birth, including the medication name, start and stop dates, and frequency of use. If the mother reported use of an antihypertensive medication but did not recall the medication name, a list of commonly prescribed antihypertensive medications was read to her. All of the medication exposures were coded using the Slone Epidemiology Center Drug Dictionary. To be considered exposed to an antihypertensive medication, mothers must have reported both a diagnosis of high blood pressure and use of a medication that was classified as an antihypertensive medication at any time from 1 month before pregnancy to birth. Medications were categorized into antiadrenergic agents (centrally acting antiadrenergic agents or

β -blockers), ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, and direct vasodilators. Because ACE inhibitors and angiotensin II receptor blockers have a similar mechanism of action, a category that included both classes was created. Two windows of exposure were assessed. “First-trimester use” was defined as any use from 1 month preconception through the third month of pregnancy. “Late initiation” was defined as any use initiated after the first trimester. Women reporting high blood pressure during pregnancy without medication use were classified as having “untreated hypertension,” and women not reporting high blood pressure or medication use were considered unexposed.

Exclusions

Of the 5608 CVM case infants and 5008 control infants, we excluded 388 cases (6.9%) and 152 controls (3.0%) who were multiple births and 162 cases (2.9%) and 25 controls (0.5%) whose mothers reported preexisting type 1 or 2 diabetes mellitus. Additional exclusions were made for 26 case mothers (0.5%) and 25 control mothers (0.5%) without hypertension who reported a medication with antihypertensive properties that was used for another indication and 11 case mothers (0.2%) and 10 control mothers (0.2%) with missing hypertension diagnosis or medication date data. Because ascertainment periods for pulmonary valve stenosis (PVS) varied by study center, exclusions of cases and controls were made for certain study centers and time periods.

Statistical Analysis

Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between antihypertensive medication treatment and the occurrence of CVMs while controlling for confounding variables. Each model included the study center. The potential confounders and effect modifiers evaluated were maternal age at delivery, education, race/ethnicity, parity, prepregnancy body mass index (weight in kilograms per height in meters squared), gestational diabetes, use of fertility medications or procedures, and fever or nausea/vomiting during the first trimester. We also examined smoking and use of caffeine, alcohol, cocaine, or crack; vasoactive medications (amphetamines, decongestants, bronchodilators, ibuprofen, aspirin, other nonsteroidal anti-inflammatory medications, and antimigraine medications); anticonvulsants; oral contraceptives; and folic acid/multivitamins during the periconception period. Backward selection was used to eliminate variables from a full model, which included potential confounders identified in bivariate analyses. Variables causing a $\geq 10\%$ change in the OR estimate for antihypertensive medication use were retained in the model. To simplify the presentation of results, 4 covariates were used in the final models: study center, maternal age at delivery, prepregnancy body mass index, and gestational diabetes. For birth defects with <5 exposed cases, crude ORs and exact 95% CIs were calculated.

We conducted 2 types of analyses: analyses of associations reported previously in the literature (“hypothesis testing”) and exploratory analyses (“hypothesis generation”). To test the hypothesis that ACE inhibitors increase the risk of CVMs,^{21,22} we compared the relationship between first-trimester use of ACE inhibitors or other antihypertensive medications and the risk of CVMs. In addition, we examined the risk of CVMs in relation to first-trimester exposures to antiadrenergic agents (including β -blockers),^{22,25} diuretics,^{24,25} and calcium channel blockers.^{22,26} To generate hypotheses, we compared the risks of specific CVMs in relation to first-trimester use of antihypertensive medications, late initiation of medications, and untreated hypertension. We analyzed 8 broad groups of CVMs (heterotaxy/situs inversus, single ventricle, conotruncal defects, atrioventricular septal defect, anomalous pulmonary venous return, RVOTO, LVOTO, and septal defects), as well as defects with ≥ 100 subjects or any defect with ≥ 3 exposed subjects. Cases recorded as “atrial septal defect (ASD) not otherwise specified” were considered as probable cases of secundum ASD and were counted as such in the main analyses; subanalyses were performed without these cases. To consider potential confounding by underlying hypertension, we estimated CVM risks in women with late initiation of medications and untreated hypertension. For the

Table 1. Selected Maternal and Infant Characteristics of Cardiovascular Malformation Cases and Nonmalformed Controls: the NBDPS, October 1997 to December 2003

Variable	Any Study CVM (n=5021), n (%) [*]	Controls (n=4796), n (%) [*]
Infant sex		
Male	2665 (53.1)	2421 (50.5)
Female	2351 (46.9)	2370 (49.5)
Maternal age at delivery, y		
<20	522 (10.4)	547 (11.4)
20 to 34	3730 (74.3)	3614 (75.4)
≥35	769 (15.3)	635 (13.2)
Parity		
0	2030 (40.5)	1935 (40.4)
1	1646 (32.8)	1647 (34.4)
≥2	1338 (26.7)	1206 (25.2)
Race/ethnicity		
Non-Hispanic white	3010 (60.0)	2863 (59.9)
Non-Hispanic black	614 (12.3)	558 (11.7)
Hispanic	1110 (22.1)	1098 (23.0)
Other	280 (5.6)	265 (5.5)
Prepregnancy body mass index†		
Underweight	286 (5.9)	276 (6.0)
Normal	2494 (51.7)	2608 (56.7)
Overweight	1155 (24.0)	1015 (22.1)
Obese	885 (18.4)	698 (15.2)
Gestational diabetes		
Yes	397 (7.9)	256 (5.3)
No	4613 (92.1)	4536 (94.7)
Preterm birth (<37 wk)		
Yes	1039 (20.7)	381 (8.0)
No	3979 (79.3)	4412 (92.1)

^{*}Totals for each characteristic vary because of missing values.

†Data were calculated as weight in kilograms divided by height in meters squared (classification of the National Institutes of Health).

CVM groups found to be associated with medication use, we assessed medication classes and specific medications (where numbers permitted). Subanalyses of term births were performed to examine whether the observed associations were likely attributable to increased detection of CVMs among preterm infants who are more likely to undergo echocardiography in the neonatal intensive care unit.³¹ Additional analyses excluded infants with a family history of a heart defect in a first-degree relative. Data analyses were performed using SAS 9.1 (SAS Institute).

Results

Interview data for 5021 CVM case infants and 4796 control infants were included in these analyses. Compared with mothers of control infants, mothers of infants with CVMs were more likely to be older, heavier, and to develop gestational diabetes; higher proportions of male and preterm births were found among case infants (Table 1).

Overall, 552 case mothers (11.0%) and 427 control mothers (8.9%) reported high blood pressure during the study pregnancy; of those women, 22.1% and 14.3% reported

Table 2. Adjusted ORs for the Association Between First-Trimester Use of ACE Inhibitors or Other Antihypertensive Medication Classes and the Risk of Cardiovascular Malformations: the NBDPS, October 1997 to December 2003

First-Trimester Use	Controls (n=4796), n	Any Study CVM (n=5021), n	OR (95% CI) [*]
ACE inhibitors	3	8	1.9 (0.5 to 7.2)
Other medication classes	27	56	1.7 (1.1 to 2.8)
Antiadrenergic agents	24	51	1.8 (1.1 to 2.9)
β-Blockers	10	31	2.6 (1.2 to 5.3)
Calcium channel blockers	6	8	1.0 (0.3 to 3.0)
Diuretics	1	8	5.5 (0.7 to 44.6)

^{*}Reference group indicated no history of hypertension. ORs were adjusted for study center, maternal age at delivery (<35 years or ≥35 years), prepregnancy body mass index (underweight/normal or overweight/obese), and gestational diabetes.

medication treatment, respectively. For the period 1 month preconception through birth, 122 case mothers (2.4%) and 61 control mothers (1.3%) reported taking an antihypertensive medication, and for both case and control mothers, the proportions increased throughout pregnancy.

Among women who reported antihypertensive medication use any time during pregnancy, approximately half reported use during the first trimester (64 cases and 30 controls), and half reported initiating treatment after the first trimester (58 cases and 31 controls). Few women who reported first-trimester medication use discontinued treatment before the second trimester (7 cases: 6 β-blockers and 1 ACE inhibitor; 3 controls: 2 calcium channel blockers and 1 diuretic). Methyldopa, a centrally acting antiadrenergic agent, was the most frequently reported medication during both periods for women continuing preconception treatment, initiating treatment, or changing treatment from other medication classes during early pregnancy. Although ACE inhibitors and angiotensin II receptor blockers are contraindicated during the second and third trimesters, 6 case mothers (2 perimembranous ventricular septal defects [VSDs], 2 secundum ASDs, 1 VSD-ASD association, and 1 tetralogy of Fallot) and no control mothers reported use of those medications during those periods.

Hypothesis Testing

Table 2 shows the ORs for CVMs overall according to first-trimester maternal use of antihypertensive medication classes that have been reported to be associated with an increase in CVMs. Estimates for CVMs were elevated in women reporting ACE inhibitor use (adjusted OR: 1.9; 95% CI: 0.5 to 7.2), but the CI was wide and included the null value. Significant increases in the risk of CVMs (ranging from 1.7 to 2.6) were detected in relation to the use of other medication classes combined, the subgroup of antiadrenergic agents, and, specifically, β-blockers.

Hypothesis Generation

Table 3 shows the relationships among first-trimester use of antihypertensive medications, late initiation of medications,

Table 3. Adjusted ORs for the Association Between First-Trimester Use of Antihypertensive Medication, Late Initiation of Antihypertensive Medication, or Untreated Hypertension and the Risk of Cardiovascular Malformations: the NBDPS, October 1997 to December 2003

CVM Group	Total	First-Trimester Use		Late Initiation*		Untreated Hypertension	
		N	OR (95% CI)†	N	OR (95% CI)†	N	OR (95% CI)†
Controls‡	4796	30		31		365	
Any study CVM	5021	64	1.8 (1.1 to 2.7)	58	1.7 (1.1 to 2.6)	429	1.1 (0.9 to 1.3)
Heterotaxy/situs inversus	148	2	2.1 (0.2 to 8.4)	1	1.0 (0.1 to 6.2)	6	0.6 (0.2 to 1.3)
Single ventricle	156	0		0		14	1.1 (0.6 to 2.0)
Conotruncal defect	1036	8	1.0 (0.5 to 2.3)	9	1.1 (0.5 to 2.6)	86	1.1 (0.8 to 1.4)
d-Transposition of the great arteries	328	3	1.5 (0.3 to 4.8)	3	1.4 (0.3 to 4.6)	24	0.9 (0.6 to 1.4)
Tetralogy of Fallot	466	4	1.4 (0.4 to 4.0)	5	1.3 (0.5 to 3.9)	38	1.1 (0.8 to 1.6)
Atrioventricular septal defect	126	2	2.6 (0.3 to 10.3)	2	2.5 (0.3 to 9.9)	8	0.9 (0.4 to 1.9)
RVOTO	750	17	3.1 (1.7 to 5.8)	9	1.9 (0.9 to 4.2)	66	1.1 (0.9 to 1.5)
PVS	534	11	2.6 (1.3 to 5.4)	8	2.4 (1.1 to 5.4)	52	1.2 (0.9 to 1.7)
Ebstein malformation	65	4	11.4 (2.8 to 34.1)	1	2.8 (0.1 to 17.3)	9	2.1 (1.0 to 4.3)
Pulmonary atresia	102	1	1.5 (0.1 to 9.4)	0		6	0.8 (0.3 to 1.7)
LVOTO	772	9	1.7 (0.8 to 3.7)	6	1.2 (0.5 to 3.0)	64	1.1 (0.8 to 1.4)
Hypoplastic left heart syndrome	233	1	0.7 (0.1 to 4.1)	1	0.7 (0.1 to 4.0)	17	0.9 (0.6 to 1.5)
CoA	406	8	3.0 (1.3 to 6.6)	3	1.2 (0.2 to 3.8)	36	1.2 (0.8 to 1.7)
Aortic stenosis	160	0		2	2.0 (0.2 to 7.8)	14	1.0 (0.6 to 1.8)
Septal defect	2130	35	2.4 (1.4 to 4.0)	35	2.4 (1.5 to 4.0)	194	1.2 (1.0 to 1.4)
Perimembranous VSD	878	10	1.7 (0.8 to 3.5)	12	2.3 (1.2 to 4.6)	79	1.2 (0.9 to 1.5)
Secundum ASD	1137	19	2.4 (1.3 to 4.4)	19	2.4 (1.3 to 4.4)	114	1.3 (1.0 to 1.6)
Anomalous pulmonary venous return	141	1	1.1 (0.1 to 6.9)	1	1.1 (0.1 to 6.7)	10	0.9 (0.4 to 1.8)
Total anomalous pulmonary venous return	118	1	1.3 (0.1 to 8.0)	1	1.3 (0.1 to 7.8)	5	0.5 (0.2 to 1.2)

*Late initiation indicates initiation after the first trimester.

†Reference group indicates no history of hypertension. For CVMs with ≥ 5 exposed cases, ORs were adjusted for study center, maternal age at delivery (<35 years or $\geq 35+$ years), prepregnancy body mass index (underweight/normal or overweight/obese), and gestational diabetes. For CVMs with <5 exposed cases, crude ORs with exact 95% CIs were calculated.

‡There were 4335 controls in the pulmonary valve stenosis analysis because of differences in case ascertainment by study center. The numbers of exposed controls were the same.

untreated hypertension, and the risk of CVM groups. First-trimester treatment was significantly associated with the risk of PVS, Ebstein malformation, coarctation of the aorta (CoA), and secundum ASDs. Treatment initiated after the first trimester was significantly associated with PVS, perimembranous VSDs, and secundum ASDs. Untreated hypertension was significantly associated with Ebstein malformation and secundum ASDs. Models were adjusted for maternal age at delivery, prepregnancy body mass index, and gestational diabetes, in addition to study center. The ORs moved toward the null value in women reporting first-trimester or late initiation of treatment, whereas adjustment for these factors did not change the ORs in women with untreated hypertension.

For CVMs positively associated with first-trimester exposure identified in Table 3, Table 4 presents ORs for specific medication classes and for commonly reported specific medications. Among the 6 statistically significant associations, all but 2 were based on <5 exposed cases, so the effect estimates are unstable. Nevertheless, except for the class of calcium channel blockers, elevated risks for any CVM were observed for all of the medication classes and for all of the specific medications examined; among the specific defects associated with any antihypertensive use in Table 3, elevated risks were

generally observed for all of the medication classes and specific medications examined.

We also examined associations between medication classes initiated late in pregnancy and the risk of CVMs (data not shown). The initiation of centrally acting antiadrenergic agents in late pregnancy was not significantly associated with CVMs, although elevated risks were observed for PVS (OR: 3.1; 95% CI: 0.7 to 10.5; 4 exposed cases) and secundum ASDs (adjusted OR: 2.2; 95% CI: 0.9 to 5.4; 9 exposed cases). The initiation of β -blockers in late pregnancy was associated with the risk of perimembranous VSDs (OR: 5.6; 95% CI: 0.7 to 41.8; 3 exposed cases).

Because hypertension during pregnancy was associated with preterm delivery (OR: 2.1; 95% CI: 1.5 to 2.8) among control mothers, subset analyses of term births were performed to examine whether the associations detected were artifacts of prematurity (data not shown). Among term births, small attenuations in the ORs were noted for first-trimester medication use for PVS (adjusted OR: 2.2; 95% CI: 0.8 to 5.9; 5 exposed cases) and secundum ASDs (adjusted OR: 2.3; 95% CI: 1.0 to 5.3; 9 exposed cases). Greater attenuations were observed for treatment initiation in late pregnancy for PVS (OR: 1.3; 95% CI: 0.3 to 4.5; 3 exposed cases), perimembranous

Table 4. Adjusted ORs for the Association Between First-Trimester Use of Antihypertensive Medication and the Risk of Selected Cardiovascular Malformations by Medication Class: the NBDPS, October 1997 to December 2003

First-Trimester Use	Controls (n=4796), N†	RVOTO											
		Any Study CVM (n=5021)		PVS (n=534)				Ebstein Malformation (n=65)		LVOTO, CoA (n=406)		Septal Defect, Secundum ASD (n=1137)	
		N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*		
Centrally-acting antiadrenergic agent‡													
Any	15	27	1.5 (0.8 to 2.9)	3	1.7 (0.3 to 6.0)	3	16.9 (3.0 to 62.1)	4	3.2 (0.8 to 10.2)	6	1.5 (0.5 to 3.9)		
Methyldopa	13	26	1.7 (0.9 to 3.4)	3	1.9 (0.4 to 7.1)	2	12.7 (1.4 to 58.3)	4	3.7 (0.9 to 12.1)	6	1.8 (0.7 to 5.0)		
β-Blocker§													
Any	10	31	2.6 (1.2 to 5.3)	7	5.0 (1.8 to 13.8)	1	8.1 (0.2 to 58.9)	3	3.6 (0.6 to 14.1)	8	2.8 (1.1 to 7.5)		
Atenolol	5	11	1.9 (0.6 to 5.4)	2	4.2 (0.4 to 29.4)	0		1	2.4 (0.1 to 21.5)	1	0.9 (0.1 to 7.8)		
Labetalol	3	11	3.1 (0.9 to 11.2)	1	2.8 (0.1 to 34.9)	0		2	8.0 (0.7 to 70.3)	4	5.9 (1.0 to 40.1)		
Calcium channel blocker													
Any	6	8	1.0 (0.3 to 3.0)	0		0		0		5	3.4 (0.9 to 12.5)		
Diuretic¶													
Any	1	8	5.5 (0.7 to 44.6)	2	16.8 (0.9 to 994)	1	81.5 (1.0 to 6400)	1	12.0 (0.2 to 944)	3	13.2 (1.1 to 692)		
ACE inhibitor#													
Any	3	8	1.9 (0.5 to 7.2)	0		1	27.1 (0.5 to 343)	0		2	2.9 (0.2 to 25.6)		
Angiotensin II receptor blocker**													
Any	0	5		1		0		0		2			
ACE inhibitor or angiotensin II receptor blocker#**													
Any	3	13	3.2 (0.9 to 11.1)	1	2.8 (0.1 to 34.9)	1	26.4 (2.3 to 306)	0		4	5.9 (1.0 to 40.1)		

*Reference group indicates no history of hypertension. For CVMs with ≥5 exposed cases, ORs were adjusted for study center, maternal age at delivery (<35 years or ≥35+ years), prepregnancy body mass index (underweight/normal or overweight/obese), and gestational diabetes. For CVMs with <5 exposed cases, crude ORs with exact 95% CIs were calculated.

†There were 4335 controls in the pulmonary valve stenosis analysis because of differences in case ascertainment by study center. The numbers of exposed controls were the same.

‡Data include clonidine and methyldopa.

§Data include atenolol, betaxolol, bisoprolol, labetalol, metoprolol, pindolol, and propranolol.

||Data include amlodipine, diltiazem, nifedipine, nisoldipine, and verapamil.

¶Data include acetazolamide, hydrochlorothiazide, and triamterene.

#Data include benazepril, enalapril, fosinopril, lisinopril, quinapril, and ramipril.

**Data include losartan, olmesartan, and valsartan.

VSDs (OR: 0.8; 95% CI: 0.2 to 2.6; 3 exposed cases), and secundum ASDs (adjusted OR: 1.7; 95% CI: 0.7 to 4.2; 7 exposed cases). Subanalyses, which excluded infants with a family history of a CVM, did not produce results that were materially different from the full analyses.

Discussion

Hypothesis Testing

In our large, population-based, case-control study, we found that women who reported use of any antihypertensive medications during pregnancy were at an increased risk of having an infant with certain CVMs. These findings contrast with those reported by Cooper et al.²¹ In that study, first-trimester ACE inhibitor use was associated with risk of CVMs (adjusted OR: 3.7; 95% CI: 1.9 to 7.3), whereas use of other medication classes was not (adjusted OR: 0.9; 95% CI: 0.2 to 3.6), leading these authors to attribute their findings to ACE inhibitor exposure and not to the underlying hypertension. In our study, the increased risk for CVMs was not specific to first-trimester exposures to ACE inhibitors. Although we observed a modest nonsignificant elevation in the risk for all

CVMs related to first-trimester ACE inhibitor use (adjusted OR: 1.9; 95% CI: 0.5 to 7.2), we also observed increased risks (ranging from 1.5 to 5.5) associated with the use of all other medication classes except calcium channel blockers (centrally acting antiadrenergic agents, β-blockers, and diuretics). Significant associations were observed only for antiadrenergic agents and, specifically, β-blockers. Our results agree with 2 studies based on the Swedish Medical Birth Register. Lennestal et al²² reported an increased risk of CVMs in women with first-trimester exposures to antihypertensive medications that was not specific to ACE inhibitors (notably for β-blockers), and Kallen and Otterblad Olausson²⁵ reported an approximate doubling of the risk of CVMs in women with first-trimester exposures to antiadrenergic agents, β-blockers, or diuretics. Our observation of no significant association between calcium channel blockers and CVMs is similar to reports by Lennestal et al,²² Kallen and Otterblad Olausson,²⁵ and Sorensen et al.²⁶

Because of the well-known fetopathies associated with second- and third-trimester exposures to ACE inhibitors,¹⁻¹¹ Cooper et al²¹ excluded from their analysis of Tennessee

Medicaid claims data women prescribed medications beyond the first trimester to determine whether first-trimester exposure alone constituted a risk. Thus, their analysis was restricted to 209 women prescribed ACE inhibitors and 202 women prescribed other antihypertensive medications during the first trimester alone, which represented 29% of the 1414 women with prescriptions filled at any time during pregnancy in the cohort. By contrast, in our study, only 7 case mothers (6%) and 3 control mothers (5%) reporting antihypertensive treatment during pregnancy were exposed in the first-trimester alone, and only 1 subject (a case infant) was exposed to an ACE inhibitor. Thus, our data cannot contribute to resolving the question of whether ACE inhibitor exposure confined to the first trimester might increase the risk of CVMs. Because other studies similarly did not speak to this question,^{22–26} the finding from the Tennessee Medicaid data remains unconfirmed. In addition, even if the Tennessee finding is supported, its public health impact may be minimal, because our findings, based on data from 10 states, suggest that exposure to ACE inhibitors in the first trimester is a relatively unusual phenomenon.

Hypothesis Generation

In the context of multiple testing, we found increased risks of CoA, PVS, Ebstein malformation, and septal defects in mothers reporting any antihypertensive medication use. The positive association with Ebstein malformation, a rare CVM, is a new finding. This increase in women with both treated and untreated hypertension suggests that the underlying hypertension might play an etiologic role. Early medication use likely corresponds with treated chronic hypertension, whereas late initiation suggests gestational hypertension or preeclampsia. The greater risk in early medication users suggests that the combined effects of medication and hypertension are important. For PVS and septal defects, risks were increased in both early and late medication users; however, the risk estimates in late medication users were attenuated in a subanalysis of term births. For CoA, risks were increased only in early users. Of note, increased risks for these defects were not detected in women with untreated hypertension.

The observed increased risks in users of various medication classes but not in women with untreated hypertension (except for Ebstein malformation and secundum ASDs) suggest either that antihypertensive medications are teratogenic or that women taking antihypertensive medications have more severe hypertension and it is the disease severity that increases the risk of certain heart defects. Both maternal hypertension and antihypertensive medications might cause uteroplacental insufficiency, decreasing blood flow to the uterus during pregnancy,^{7–9} thus lowering fetal blood pressure. Alterations in fetal intracardiac blood flow and cell death have been proposed as 2 mechanisms of abnormal heart development.^{32,33} Some RVOTO, LVOTO, and septal defects might be caused by changes in fetal blood flow, and Ebstein malformation might be attributable to an alteration in programmed cell death. An extreme example of hemodynamic imbalance occurs in twin-to-twin transfusion syndrome.^{34–36} In studies of twin pregnancies, PVS was more common than in singleton pregnancies, particularly in recipient twins.

Ebstein malformation was also significantly more common among twin pregnancies.³⁴

The observed increased risks of certain RVOTO and septal defects in infants of women who initiated treatment after the first trimester do not preclude medications as potential etiologic agents, because some CVMs can occur beyond the first trimester.^{35–37} In prospective studies of twin pregnancies, fetuses with normal fetal pulmonary velocities in the second trimester developed neonatal PVS, suggesting that this defect might develop after the first trimester.^{35,36} Among the PVS and septal defect cases exposed to antihypertensive medications at any time during pregnancy in our study, 89.5% and 94.3% of the mothers reported medication use after the first trimester, respectively. Because knowledge about the pathogenesis of CVMs is incomplete, follow-up studies examining the relationship between late exposures and CVMs are warranted. Notably, although animal studies suggest that hypoplastic left heart syndrome, a left obstructive defect, can be induced via altered blood flow in late pregnancy, hypoplastic left heart syndrome risk was not increased in our study.³⁷

Methyldopa, atenolol, and labetalol were the most commonly reported medications in our study. Methyldopa is the preferred medication for the treatment of chronic hypertension during pregnancy based on reports of stable uteroplacental perfusion and fetal hemodynamics, as well as the absence of long-term adverse effects on development in children with in utero exposures followed up to 7.5 years.⁵ Labetalol is increasingly preferred to methyldopa because of a more favorable maternal adverse-effects profile, but long-term safety data in children do not exist.⁵ β -Blockers are considered generally safe, except for recent reports of intrauterine growth retardation related to their use.^{1–6,12–14} There are limited data on the safety of calcium channel blockers and diuretics.⁵ ACE inhibitors and angiotensin II receptor blockers were reportedly used beyond the first trimester by some women in our study, although those medication classes are contraindicated because of the risk of fetal developmental abnormalities associated with second- and third-trimester use.^{1–11}

The NBDPS included a standardized protocol for maternal interviews, which were performed within 24 months after the estimated dates of delivery and collected data for a large number of potential confounders.²⁸ Timing of medication use was available to evaluate exposures during critical developmental windows. Because our exposure assessment was based on maternal self-report, we broadly defined our first-trimester exposure period by including the month before conception. Only 2 controls reported discontinuing medication use in that 1-month period, which would have biased our estimates toward unity. Reporting inaccuracy was minimized by using indication-based prompts for medication use^{38–43}; furthermore, recall of medications is likely to be relatively accurate for prescription medications taken in early pregnancy for chronic hypertension.⁴¹ Because infants without malformations served as controls, recall bias is a concern; however, we think differential recall among case mothers compared with control mothers is not a likely explanation for our findings, because we observed associations for some CVM groups and not others and for some classes of antihypertensive medications and not others. The meticulous case

review decreased the misclassification of the cases and heterogeneity of the case groups^{28,30}; however, the sample sizes for the analyses of specific CVMs in relation to antihypertensive medication use were small, leading to imprecise estimates.

Mothers in this study were not asked about the type or severity of hypertension (eg, chronic versus preeclampsia and mild versus severe) or medication dose, limiting our ability to address confounding by indication. The observed pattern of higher risk estimates for women with treated hypertension compared with those who were untreated might represent an effect of medication use, more severe disease, or a combination of the two.^{38,40,44}

Perspectives

The results of this large case-control study of CVMs suggest that medication use for maternal hypertension might increase the risk of having an infant with specific left and right obstructive and septal defects. For the most part, however, the risks that we observed were modest and must be weighed against health risks associated with untreated hypertension. Despite the large size of the NBDPS, the relatively infrequent use of many medications limited our ability to examine the risks and safety of specific medications in relation to specific defects; we have included results based on small numbers of exposed subjects to allow other researchers to compare their observations to ours. Finally, because many statistical tests were performed, some of our findings, particularly those related to hypothesis generation, might be attributable to chance. Therefore, the results must be interpreted with caution, and further studies with adequate power will be needed to follow up on these findings.

Acknowledgments

We thank the participating families, staff, and scientists from all of the National Birth Defects Prevention Study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Coding of drug information in the study used the Slone Epidemiology Center Drug Dictionary, under license from the Slone Epidemiology Center at Boston University. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Source of Funding

This research was supported by a cooperative agreement with the Centers for Disease Control and Prevention (grant U50CCU213244).

Disclosures

A.E.L. has provided limited consultation for 2 law firms in the United States about birth defects and environmental exposures, which did not involve drugs in this study. The Slone Epidemiology Center at Boston University receives support from drug companies for unrelated work. However, the companies may make products covered in this article. A.A.M. has consulted with a United Kingdom law firm on antiepileptic drugs and birth defects. M.M.W. receives honoraria from the National Institutes of Health and from Abbott Laboratories for advisory work on a pregnancy registry study for Humira. She also participates on advisory boards for Abbott, Aventis, and Amgen on pregnancy registry studies of drugs for rheumatoid arthritis. The remaining authors report no conflicts.

References

1. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol.* 2000;183:S1–S22.
2. Afifi Y, Churchill D. Pharmacological treatment of hypertension in pregnancy. *Curr Pharm Des.* 2003;9:1745–1753.
3. Magee LA. Treating hypertension in women of child-bearing age and during pregnancy. *Drug Saf.* 2001;24:457–474.
4. Mulrow CD, Chiquette E, Ferrer RL, Sibai BM, Stevens KR, Harris M, Montgomery KA, Stamm K. Management of chronic hypertension during pregnancy. *Evid Rep Technol Assess (Summ).* 2000;14:1–4.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252.
6. Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol.* 2002;100:369–377.
7. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. *Birth Defects Res A Clin Mol Teratol.* 2005;73:123–130.
8. CDC. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987–1995. *MMWR Morb Mortal Wkly Rep.* 1997;46:240–242.
9. Mastrobattista JM. Angiotensin converting enzyme inhibitors in pregnancy. *Semin Perinatol.* 1997;21:124–134.
10. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev.* 2006;82:23–28.
11. Schaefer C. Angiotensin II-receptor-antagonists: further evidence of fetotoxicity but not teratogenicity. *Birth Defects Res A Clin Mol Teratol.* 2003;67:591–594.
12. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ.* 1990;301:587–589.
13. Briggs GG, Freeman RK, Yaffe SJ. Atenolol. *Drugs in Pregnancy and Lactation Update.* 2003;16:10–15.
14. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens.* 1999;12:541–547.
15. Ananth CV, Peedicayil A, Savitz DA. Effect of hypertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational-age births. *Epidemiology.* 1995;6:391–395.
16. Haelterman E, Breart G, Paris-Llado J, Dramaix M, Tchobrousky C. Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth. *Am J Epidemiol.* 1997;145:689–695.
17. Ridings JE, Palmer AK, Davidson EJ, Baldwin JA. Prenatal toxicity studies in rats and rabbits with the calcium channel blocker diproteverine. *Reprod Toxicol.* 1996;10:43–49.
18. Reprotox. An information system on environmental hazards to human reproduction and development. Reserpine. 2001. Available at: <http://www.reprotox.org>. Accessed April 20, 2005.
19. Schardein JL. *Chemically Induced Birth Defects*. 3rd ed. New York, NY: Marcel Dekker, Inc; 2000:517–557.
20. Scott WJ Jr, Resnick E, Hummler H, Clozel JP, Burgin H. Cardiovascular alterations in rat fetuses exposed to calcium channel blockers. *Reprod Toxicol.* 1997;11:207–214.
21. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med.* 2006;354:2443–2451.
22. Lennestall R, Otterblad Olausson P, Kallen B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *Eur J Clin Pharmacol.* In press.
23. Ferencz C, Rubin JD, Loffredo CA, Magee CA, eds. *Epidemiology of Congenital Heart Disease: The Baltimore-Washington Infant Study 1981–89*. Mount Kisco, NY: Futura Publishing Co; 1993.
24. Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton, CO: PSG Publishing Co; 1977.
25. Kallen BA, Otterblad Olausson P. Maternal drug use in early pregnancy and infant cardiovascular defect. *Reprod Toxicol.* 2003;17:255–261.

26. Sorensen HT, Czeizel AE, Rockenbauer M, Steffensen FH, Olsen J. The risk of limb deficiencies and other congenital abnormalities in children exposed in utero to calcium channel blockers. *Acta Obstet Gynecol Scand.* 2001;80:397–401.
27. Rasmussen SA, Lammer EJ, Shaw GM, Finnell RH, McGehee RE Jr, Gallagher M, Romitti PA, Murray JC. Integration of DNA sample collection into a multi-site birth defects case-control study. *Teratology.* 2002;66:177–184.
28. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol.* 2003;67:193–201.
29. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, Costas P, Druschel C, Hobbs CA, Romiti PA, Langlois PH, Edmonds LD. The National Birth Defects Prevention Study. *Public Health Rep.* 2001;116(suppl 1):32–40.
30. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol.* 2007;79:714–727.
31. Tanner K, Sabine N, Wren C. Cardiovascular malformations among preterm infants. *Pediatrics.* 2005;116:833–838.
32. Clark EB. Mechanisms in the pathogenesis of congenital cardiac malformations. In: Pierpont ME, Moller JH, eds. *The Genetics of Cardiovascular Disease.* Boston, MA: Martinus Nijhoff Publishing; 1986:3–11.
33. Clark EB. Pathogenetic mechanisms of congenital cardiovascular malformations revisited. *Semin Perinatol.* 1996;20:465–472.
34. Hajdu J, Beke A, Marton T, Hruba E, Pete B, Papp Z. Congenital heart diseases in twin pregnancies. *Fetal Diagn Ther.* 2006;21:198–203.
35. Karatza A, Wolfenden J, Taylor M, Wee L, Fisk N, Gardiner H. Influence of twin-twin transfusion syndrome on fetal cardiovascular structure and function: prospective case-control study of 136 monozygotic twin pregnancies. *Heart.* 2002;88:271–277.
36. Szewast A, Rychik JR. Current concepts in fetal cardiovascular disease. *Clin Perinatol.* 2005;32:857–875.
37. deAlmeida A, McQuinn T, Sedmera D. Increased ventricular preload is compensated by myocyte proliferation in normal and hypoplastic fetal chick left ventricle. *Circ Res.* 2007;100:1363–1370.
38. Kallen BA. Methodological issues in the epidemiological study of the teratogenicity of drugs. *Congenit Anom (Kyoto).* 2005;45:44–51.
39. Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *Am J Epidemiol.* 1986;123:670–676.
40. Mitchell AA. Special considerations in studies of drug-induced birth defects. In: Strom BL, ed. *Pharmacoepidemiology.* New York, NY: John Wiley & Sons, Ltd; 2000:749–763.
41. Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sorensen HT. Recall bias in a case-control surveillance system on the use of medicine during pregnancy. *Epidemiology.* 2001;12:461–466.
42. Swan SH, Shaw GM, Schulman J. Reporting and selection bias in case-control studies of congenital malformations. *Epidemiology.* 1992;3:356–363.
43. Werler MM, Pober BR, Nelson K, Holmes LB. Reporting accuracy among mothers of malformed and nonmalformed infants. *Am J Epidemiol.* 1989;129:415–421.
44. Ward RM. Difficulties in the study of adverse fetal and neonatal effects of drug therapy during pregnancy. *Semin Perinatol.* 2001;25:191–195.