

Maternal Asthma, Asthma Medication Use, and the Risk of Congenital Heart Defects

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BACKGROUND: Asthma is a common problem that complicates pregnancy. Several drugs are considered acceptable for use during pregnancy, although none have been classified as safe. Few studies have assessed the health impact of maternal asthma/medication use on the fetus. **METHODS:** A population-based case-control study was conducted in New York State to determine if cardiac congenital malformations in offspring were associated with maternal use of asthma medication and/or maternal asthma. Cases were cardiac anomalies in the New York State Congenital Malformations Registry. Controls were live births without any major birth defects randomly selected from birth certificates and frequency matched by year of birth. Data were collected through a 30 min telephone interview. Exposure was maternal asthma/medication use, maternal asthma/no medication use, no asthma/medication use, and no asthma/no medication use (reference). **RESULTS:** A total of 502 (59.4%) cases and 1,066 (53.8%) controls participated. A positive association was seen between any heart defect and women with asthma who used medication (OR 2.38; 95% CI: 1.18, 4.82). No significant associations were observed between heart defects and either women with asthma who did not use medication or women without asthma who used asthma medications. When considering types of medication used, offspring of women with asthma who used bronchodilators had an increased risk of any heart defect (OR 2.20; 95%CI: 1.05, 4.61). **CONCLUSIONS:** These results suggest that both maternal asthma status (controlled vs. uncontrolled; severe vs. mild) and asthma medication use, particularly bronchodilators, may play a role in cardiac malformations in offspring. *Birth Defects Research (Part A) 85:161–168, 2009.* © 2008 Wiley-Liss, Inc.

Key words: asthma; medication; heart defects

INTRODUCTION

It is well known that asthma is a common problem that complicates pregnancy (Namazy, 2004), affecting 4–8% of all pregnancies (Osur, 2005). Many drugs are available for treating asthma with several considered acceptable for use during pregnancy. None, however, have been classified as safe for use during pregnancy. Asthma medications fall into two major categories: bronchodilators, which include both short and long term beta-2-agonists, anticholinergic drugs, and theophylline; and anti-inflammatory drugs, which include corticosteroids, mast cell stabilizers, and leukotriene modifiers. Asthma medications may be taken for respiratory conditions other than asthma and occasionally corticosteroids may be taken for other nonrespiratory conditions, such as arthritis, allergies, or skin problems.

Congenital anomalies are present in approximately 4% of livebirths (NYS CMR report). Cardiac anomalies are

the most common group of defects, making up about 40% of all defects (Romano-Zelekha, 2001). Different cardiac anomalies arise from problems in different stages and regions of the developing heart (Sakabe, 2005). The period from weeks 3–5 of gestation is believed to be the most sensitive period for cardiac development (Sadler, 2000), although heart development may not be complete until week 7 or 8 (Sadler, 2004; Kirby, 2007).

Asthma and asthma medications have been found to be associated with several pregnancy outcomes, including congenital malformations. One recent study found a

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significantly elevated risk of any heart malformation among mothers exposed to anti-asthmatic medications. The risk was higher among women who took three or more anti-asthmatic medications, which the authors suggested may indicate more severe asthma (Kallen and Olausson, 2007). In the late 1970s three studies in chick embryos suggested the asthma medication theophylline was a cardiovascular teratogen inducing such defects as double outlet right ventricle, truncus arteriosus, and aortic arch anomalies (Park, 1990). Also, the 1990 case report by Park et al. proposed that congenital cardiac anomalies in humans may be linked to theophylline, citing the animal evidence and a series of three case reports. Furthermore, data from the Michigan Medicaid Study suggest theophylline may be associated with heart defects (Rosa, 1999). However, several other studies found no association between theophylline and congenital malformations in general (Osur, 2005). Several other studies have also failed to find an association between asthma medications and congenital anomalies (Schatz, 1995, 1997; Perlow, 1992). Although evidence is mixed, the prevailing advice in the literature is to treat the pregnant asthmatic to control the asthma symptoms (Osur, 2005; Jadad, 2000). Only one of the previous epidemiological studies attempted to look at defects of a specific organ system and none of them separated the effects of asthma medication from asthma itself. The purpose of this study was to determine if cardiac congenital malformations in offspring were associated with maternal asthma and/or asthma medication use. Although these data were collected several years ago, cardiac defects remain the most common birth defects. Furthermore, many of the asthma medications used, such as albuterol and prednisone, are still in use today.

METHODS

Study Design and Study Population

This study was based on a large population-based case-control study conducted in New York State (NYS) that was originally designed to investigate the effect of volatile organic compounds and other risk factors on congenital cardiac malformations (Agency for Toxic Substances and Disease Registry, 2004). Due to the extent of exposure information collected, it was possible to use this dataset to study the association between asthma/asthma medication use and heart defects.

The study population included all liveborn infants born during the period 1988–1991 to mothers living in one of 14 NYS counties. All major urban/suburban areas of NYS, exclusive of New York City, were included (Buffalo, Rochester, Syracuse, Albany [Capital District], Long Island, and Yonkers), as well as two New York City boroughs (Queens and Staten Island). Together these areas have approximately 140,000 births per year. The areas selected provide ethnic and racial diversity and encompass a wide geographic area.

Cases were obtained from the NYS Congenital Malformations Registry (CMR). A total of 33 British Pediatric Codes for cardiac anomalies that are routinely diagnosed and treated in hospitals prior to the age of 2 were included in the study. Cases were confirmed through review of medical records by the Medical Director of the CMR, in consultation with a pediatric cardiologist from

Albany Medical Center. All diagnoses must have been confirmed through cardiac catheterization, surgery, or echocardiogram. Cases with a confirmed chromosomal anomaly were excluded because of potential bias due to selective diagnosis and termination of pregnancies affected by genetic defects.

Controls were livebirths without any major birth defects, randomly selected from birth certificates in the 14 study counties and frequency matched by year of birth. Controls were selected in approximately a two to one ratio. Selected controls were checked against the CMR and any matches were excluded. Exclusions were replaced with another randomly selected control. Other exclusions applied to both cases and controls included the following: adopted or foster children, deceased mothers, mothers who did not speak English, Spanish, Chinese, or Korean, and residents of other counties or states at the time of birth.

Data Collection

The CMR is a population-based registry encompassing all NYS residents. Children diagnosed with a congenital anomaly up to the age of 2 years are included in the CMR. CMR records are linked to the birth certificate to verify/correct information and eliminate duplicate records. Information available through the CMR and birth certificates includes the British Pediatric Code of the anomaly, socio-demographic data (including maternal race, ethnicity, age), and maternal behaviors during pregnancy (including smoking, alcohol and vitamin use).

Names and addresses of potential study participants were taken from birth certificates. Medical records, telephone books, and Department of Motor Vehicle information were used to update addresses if possible. Physicians who reported the cases to the CMR were contacted to inform them about the study and to ask them if there was a reason the mother should not be contacted. In seven cases, the physician requested that the mother not be contacted.

A solicitation letter was sent to all remaining cases and controls describing the study. To assist with recall, the mailing also included an individualized calendar highlighting the period 1 month prior to conception through the birth of the child, based on birth certificate data. Finally, the letter included a postage paid postcard asking mothers to return it, providing a phone number and best time to call for a 30 min telephone interview. Non-responders were mailed a second packet by registered mail or called directly, if a valid phone number could be obtained. If no valid phone number could be obtained, two additional letters were sent to the last known address. If a phone number was obtained, women were called until they either consented to or refused an interview. Participants were contacted within 2 years of the birth of the child.

Data were collected during the 30 min telephone interview. The first steps in the interview process were to obtain informed consent, verify address, and confirm the dates of pregnancy retrieved from the birth certificate. The interview focused on four defined stages of the index pregnancy: (1) "before", from 1 month prior to pregnancy through the day the mother knew she was pregnant (confirmed by home pregnancy test or physician's

office test); (2) "early", the date she knew she was pregnant until the end of the first trimester; (3) the second trimester; and (4) the third trimester. For our purposes, the before stage and the early stage were combined into the periconceptional period. Because the window of fetal cardiac development likely occurred around the time that most women found out they were pregnant, relevant exposures could have occurred in either the before or early stage. Furthermore, because most women who took asthma medication in the before stage continued taking it in the early stage, combining these two periods into one should reduce the uncertainty of timing of exposure. Data collected through the interview included parents' socio-demographics, as well as detailed information about the mother's experience during the "before" and "early" stages, such as residential history, including water sources used and nearby business/industry; work history, including volunteer or school work; activities, hobbies, and crafts; products used, including cleaners, personal care items, and vitamins; and consumption of caffeine, alcohol, tobacco, and drugs. The questionnaire also asked about pregnancy complications, family history of congenital defects, and maternal medical history, including diseases/conditions and medication use during each of the four stages of pregnancy.

Congenital Heart Defects

Because different heart malformations may have different etiologies, it was useful to subcategorize some heart defects into groups that have been commonly used in heart malformation research: obstructive defects and conotruncal defects. Obstructive heart defects have an obstruction of blood flow from either the left or right side of the heart or the great vessels, including pulmonary valve atresia, tricuspid atresia/stenosis, aortic stenosis, hypoplastic left heart syndrome, subaortic stenosis, coarctation of aorta, and interruption of the aortic arch. Conotruncal defects are related to the outflow tract of the heart and include common truncus, aortic septal defect, transposition of the great vessels, tetralogy of Fallot, and tricuspid atresia/stenosis. We also used a category labeled all hearts, which includes the defects listed above as well as the following: Fallot's pentalogy, common ventricle, endocardial cushion defects, single common atrium, common atrioventricular canal, two-chambered heart, cor triatrium, Ebstein's anomaly, pulmonary infundibular stenosis, hypoplasia of aortic arch, double aortic arch, overriding aorta, persistent convolutions of aortic arch, aortic atresia, aortic hypoplasia, aortic stenosis, total anomalous pulmonary venous return, and aberrant subclavian artery.

Exposure

Exposure was divided into four groups: maternal asthma with medication use, maternal asthma without medication use, medication use without asthma, and no asthma/no medication use. Asthma medication use included bronchodilators and/or anti-inflammatories. These two broad categories were used because of small numbers of users of specific drugs in most instances. The exceptions were two specific bronchodilators that were analyzed separately: Ventolin (albuterol) was used most

commonly and previous literature suggested that Theophylline may be a teratogen. In addition, we also examined simultaneous use of multiple asthma medications as another exposure indicator to assess a potential exposure-response relationship. The group of women with no asthma who did not use asthma medication was used as the comparison group for all exposure indicators because this group was exposed to neither of our exposures of interest.

Statistical Analysis

Frequencies and proportions of demographic variables and selected other variables, by case-control status, were determined in order to describe the population. Crude ORs and 95% CIs were calculated to estimate potential effects. Any variable found to be related to exposure or disease was considered a potential confounder and included in subsequent analyses.

Unconditional logistic regression analysis was used to calculate ORs to estimate the risk of congenital heart defects for the various exposure groups. The confounder set used in the models was chosen to be complete based on the bivariate analysis and literature review. Results were similar between the parsimonious models and the full models included here. Final models were adjusted for sex of child, maternal history of pre-existing diabetes, child's family history (mother, father, sibling) of having a congenital heart defect, maternal caffeine use (use of coffee, tea, cola, or cocoa), maternal fever (associated with infectious diseases), prenatal vitamin use, and trihalomethane exposure. Trihalomethane exposure calculations are discussed in detail elsewhere (Agency for Toxic Substances and Disease Registry, 2004). Briefly, it is the level reported through routine monitoring, weighted by the amount of time the mother spent at each address where she lived. In the model, caffeine use, fever, vitamin use, and trihalomethane exposure are specific to the periconceptional period. Other confounders considered were maternal age at delivery, race, ethnicity, and body mass index (high = greater than or equal to 25 vs. normal/low = less than 25).

RESULTS

A total of 502 (59.4%) of 845 eligible cases and 1,066 (53.8%) of 1,980 controls completed the interview and were included in the final analysis. Table 1 shows the descriptive statistics, including demographic information, by case-control status, for the study population. Overall, mothers were mostly White, non-Hispanic, and between the ages of 20 and 34. In a crude analysis, maternal chronic diabetes and a family history of congenital heart defects were strongly associated with congenital heart defects. In addition, male infant sex, maternal caffeine use, and maternal fever during early pregnancy were also positively associated with having a congenital heart defect.

Table 2 presents the medications used, by case-control status. Most of the asthma medications used by study participants fall into the category of bronchodilators. A total of 75 participants (32 cases and 43 controls) used asthma medications, with 18 people (nine cases and nine controls) using more than one. Among cases using medi-

Table 1
Maternal Characteristics and Congenital Heart Defects

Variable	Cases (<i>n</i> = 502)		Controls (<i>n</i> = 1,066)		Crude O.R. (95% CI)
	<i>n</i> (%)		<i>n</i> (%)		
Maternal diabetes (pre-existing)					
Yes	17 (3.4)		9 (0.8)		4.11 (1.82, 9.28)
No	485 (96.6)		1055 (99.0)		1.00 (Reference)
Family history of congenital heart defects					
Yes	51 (10.2)		32 (3.0)		3.63 (2.30, 5.73)
No	448 (89.2)		1021 (95.8)		1.00 (Reference)
Maternal caffeine use during periconceptual period					
Ever	453 (90.2)		912 (85.6)		1.55 (1.10, 2.20)
Never	47 (9.4)		147 (13.8)		1.00 (Reference)
Maternal fever during periconceptual period					
Yes	51 (10.2)		64 (6.0)		1.83 (1.24, 2.69)
No	404 (80.5)		927 (87.0)		1.00 (Reference)
Prenatal vitamin use during periconceptual period					
Yes	126 (25.1)		289 (27.1)		0.91 (0.71, 1.17)
No	330 (65.7)		691 (64.8)		1.00 (Reference)
Trihalomethane exposure during periconceptual period					
High	92 (18.3)		214 (20.1)		0.99 (0.73, 1.34)
Medium	77 (15.3)		150 (14.1)		1.18 (0.84, 1.64)
Low	88 (17.5)		163 (15.3)		1.24 (0.90, 1.70)
None	161 (32.1)		369 (34.6)		1.00 (Reference)
Maternal age at delivery					
14–19	16 (3.2)		38 (3.6)		0.87 (0.48, 1.58)
20–34	411 (81.9)		850 (79.7)		1.00 (Reference)
35+	74 (14.7)		177 (16.6)		0.86 (0.64, 1.16)
Maternal race					
White	424 (84.5)		870 (81.6)		1.00 (Reference)
Black	32 (6.4)		100 (9.4)		0.66 (0.43, 0.99)
Other	46 (9.2)		96 (9.0)		0.98 (0.68, 1.42)
Maternal ethnicity					
Hispanic	35 (7.0)		70 (6.6)		1.07 (0.70, 1.63)
Non-Hispanic	465 (92.6)		994 (93.3)		1.00 (Reference)
Maternal body mass index					
High (≥ 25)	115 (22.9)		198 (18.6)		1.30 (1.01, 1.69)
Normal/low	387 (77.1)		868 (81.4)		1.00 (Reference)
Infant sex					
Male	329 (65.5)		579 (54.3)		1.60 (1.28, 1.99)
Female	173 (34.5)		487 (45.7)		1.00 (Reference)

Table 2
Types of Asthma Medication Used from 1 Month Prior to Conception through the End of the Third Pregnancy Month, by Case-Control Status*, Out of 502 Cases and 1,066 Controls

Medication	Cases, <i>n</i> = 32		Controls, <i>n</i> = 43	
	<i>n</i>	(%)	<i>n</i>	(%)
Bronchodilators				
Ventolin	17	(53.1)	18	(41.9)
Decongestant (nos)/bronchodilators (nos)	8	(25.0)	10	(23.3)
Theo-Dur/Theograd/Theophylline	4	(12.5)	10	(23.3)
Alupent	1	(3.1)	1	(2.3)
Primatene	1	(3.1)	1	(2.3)
Aminophylline	1	(3.1)	0	–
Brethine/Terbutalin	1	(3.1)	0	–
Epinephrine (Adrenaline)	0	–	1	(2.3)
Anti-inflammatories				
Steroids/topical cortisone cream (nos)	4	(12.5)	5	(11.6)
Prednisone	3	(9.4)	6	(14.0)
Vanceril	1	(3.1)	0	–

*Individuals may take more than one of the listed medications.

Table 3
ORs for Asthma and Medication Use (during the Periconceptional Period*) Status, by Various Heart Defect Groups

	ORs (95% CIs) [†]						
	Controls	Cases	All heart defects	Cases	Conotruncals	Cases	Obstructives
Medication use, asthma	23	24	2.38 (1.18, 4.82)	7	0.66 (0.15, 2.96)	15	4.55 (2.10, 9.82)
No medication use, asthma	56	27	1.32 (0.73, 2.39)	7	1.01 (0.41, 2.49)	16	1.61 (0.75, 3.45)
Medication use, no asthma	8	4	0.58 (0.12, 2.87)	3	1.53 (0.30, 7.73)	1	–
No medication, no asthma	965	443	1.00 (Reference)	203	1.00 (Reference)	176	1.00 (Reference)

*Periconceptional period is defined as 1 month prior to conception through the end of the third pregnancy month.

[†]ORs are all adjusted for sex of child, maternal history of chronic diabetes, family history of child with congenital heart defect, maternal caffeine use, maternal fever, prenatal vitamin use, and trihalomethane exposure.

cation, 78% used bronchodilators only, 16% used anti-inflammatories only, and 6% used a combination of bronchodilator and anti-inflammatory. Among controls using medication, 74% used bronchodilators only, 23% used anti-inflammatories only, and 2% used a combination of bronchodilator and anti-inflammatory.

Overall, 8.6% of study participants reported having asthma at the time of their pregnancy, which is consistent with the literature, although on the high side. However, only 4.8% of study participants used asthma medications at any time during pregnancy (38.5% of women with asthma). In addition, 1.6% of women with no asthma reported using at least one asthma medication (60.9% used an anti-inflammatory: prednisone [*n* = 6] or a steroid cream [*n* = 8]), and 39.1% used a bronchodilator (decongestant [*n* = 7] or Ventolin [*n* = 2]). Table 3 shows ORs and 95% CIs for the association between congenital heart defects and various combinations of asthma and asthma medication use. In addition to all heart defects, results for each of the subgroups of heart defects (conotruncals and obstructives) are presented, adjusted for potential confounders. We only present results for women who took medication beginning in the periconceptional period. The strongest associations found were

between heart defects and asthma with asthma medication use, specifically obstructive defects, when medication was started in the periconceptional period. In addition, there may also be an association between obstructive defects and asthma without asthma medication use, although the 95% CIs include the null. It was not possible to estimate the association between these defects and no asthma with medication use because of small sample sizes. No other categories displayed significantly elevated ORs.

Table 4 shows ORs and 95% CIs for the two major asthma medication classes and for two specific bronchodilators for each heart defect group. Obstructive defects are elevated among women with asthma who used bronchodilators only. The elevated risks remained significant when restricted to Ventolin use. No elevated ORs were observed among those who used anti-inflammatories only.

Table 5 shows the ORs for the association between congenital heart defects and asthma medication use categories (number of medications and duration of use during pregnancy) among asthmatics. A trend was found for the number of medications used, with multiple medication use having the strongest associations.

Table 4
ORs and 95% CIs for Types of Medication Used during the Periconceptional Period with and without Asthma and Various Heart Defect Groups

Type of medication	ORs (95% CIs) [*]						
	Controls	Cases	All heart defects	Cases	Conotruncals	Cases	Obstructives
Bronchodilators							
Bronchodilator only [†] , no asthma	1	1	–	1	–	0	–
Bronchodilator only [†] , asthma	22	22	2.20 (1.05, 4.61)	7	0.70 (0.16, 3.14)	14	4.49 (2.03, 9.94)
Ventolin use [‡] , asthma	14	15	2.37 (0.90, 6.23)	5	0.62 (0.08, 5.12)	9	4.62 (1.66, 12.85)
Theophylline use [§] , asthma	10	4	1.28 (0.36, 4.50)	0	–	4	2.44 (0.65, 9.15)
Anti-inflammatories							
Anti-inflammatory only , no asthma	7	3	0.34 (0.04, 2.93)	2	0.98 (0.11, 8.46)	1	–
Anti-inflammatory only , asthma	0	1	–	0	–	0	–
No medication, no asthma	965	443	1.00 (Reference)	203	1.00 (Reference)	176	1.00 (Reference)

*ORs are all adjusted for sex of child, maternal history of chronic diabetes, family history of child with congenital heart defect, maternal caffeine use, maternal fever, prenatal vitamin use, and trihalomethane exposure.

[†]One or more bronchodilators were used, but no anti-inflammatories.

[‡]Ventolin used alone or in combination with another bronchodilator or an anti-inflammatory (16 Ventolin only, 12 Ventolin with another bronchodilator, 1 Ventolin with an anti-inflammatory).

[§]Theophylline used alone or in combination with another bronchodilator or an anti-inflammatory (two Theophylline only, 11 theophylline with another bronchodilator, 1 Theophylline with an anti-inflammatory).

^{||}One or more anti-inflammatories were used, but no bronchodilators.

Table 5
Adjusted* ORs for the Risk of Congenital Heart Malformations among Offspring of Women with Asthma, by Medication Use Status

	ORs (95% CIs)*						
	Controls	Cases	All heart defects	Cases	Conotruncals	Cases	Obstructives
Number of medications [§]							
Non-users	56	27	1.32 (0.73, 2.39)	7	1.01 (0.41, 2.49)	16	1.61 (0.75, 3.45)
Multiple users	9	8	2.58 (0.81, 8.23)	1	–	6	3.89 (1.11, 13.59)
Duration of use during pregnancy							
Less than throughout [†]	11	10	2.25 (0.80, 6.38)	4	1.52 (0.31, 7.37)	4	2.77 (0.76, 10.16)
Throughout [‡]	15	16	2.50 (1.06, 5.86)	5	0.97 (0.20, 4.55)	11	4.95 (1.98, 12.37)
No medication, no asthma	965	443	1.00 (Reference)	203	1.00 (Reference)	176	1.00 (Reference)

*ORs are all adjusted for sex of child, maternal history of chronic diabetes, family history of child with congenital heart defect, maternal caffeine use, maternal fever, prenatal vitamin use, and trihalomethane exposure.

[†]Defined as not reporting medication use in all time periods of exposure assessment (before pregnancy recognition, after pregnancy recognition, second trimester, third trimester).

[‡]Defined as reporting medication use in all time periods of exposure assessment (before pregnancy recognition, after pregnancy recognition, second trimester, third trimester).

[§]Used during the periconceptional period.

DISCUSSION

Having a child with a congenital heart defect (specifically obstructive defects) was associated with mothers with asthma who took asthma medication during the periconceptional period (which corresponds to the critical window of cardiac development; Sadler, 2000), specifically bronchodilators. This is consistent with the findings of Kallen and Olausson (2007), who found that heart defects were associated with taking anti-asthmatic medication, specifically salbutamol (albuterol). However, that study had no data on asthma status. We observed an association between heart defects and mothers with asthma who did not take medication, but the 95% CI included the null.

We did not observe an association between medication use without asthma and heart defects, but our sample size was limited. Most of the women who did not have asthma but used medication were on anti-inflammatories (61%). Similarly, most of the anti-inflammatory users did not have asthma (78%). We did not observe an association between heart defects and taking anti-inflammatories, and were unable to restrict this analysis to only those women with asthma due to small numbers.

Inhaled beta agonists can be used intermittently for relieving symptoms and exacerbations of asthma (National Asthma Education and Prevention Program, 1993). Women who had asthma and who used a bronchodilator(s) only (suggesting uncontrolled asthma, $n = 44$) had an OR of 2.20 (1.05, 4.61) for all heart defects. The most commonly used drug in this group was Ventolin (albuterol). Ventolin was used in combination with other drugs 44.8% of the time; many of the second medications were theophylline or prednisone, which are indicated for severe asthma. Ventolin is in Pregnancy Category C because adequate human pregnancy studies are lacking even though the drug has been commonly used for decades. Albuterol has not been associated with heart defects in animals, but it has been associated with cleft palate in mice and cranioschisis in rabbits (GlaxoSmithKline, 2001).

Theophylline and prednisone (each in Pregnancy Category C: adverse effects in animals, no adequate studies in

humans) are used for treating severe asthma (National Asthma Education and Prevention Program, 1993). Furthermore, increased asthma severity is associated with taking multiple asthma medications (Mabie, 1996). Of the 14 people on theophylline in this study, all had asthma, and 12 were on another medication as well (one of those was prednisone). Compared to the reference group, women in the present study taking Theophylline ($n = 14$) had an OR of 1.28 (0.36, 4.50) for all heart defects. Although 12 of 17 multiple medication users were taking Theophylline, this result was different from the result for all multiple medication users (OR 2.58), but is consistent with Schatz (1997) and with Osur (2005) (Theophylline not associated with major defects). Because Theophylline is a strong asthma drug, often used in combination with another drug in this study (86% of the time), there may be differences within the multiple medication users group in how well asthma is controlled or asthma severity. However, we do not have direct information on symptoms or severity, so we cannot test this hypothesis.

We found that women who had asthma and used multiple asthma medications had an increased risk for having children with heart defects. This agrees with the findings of another recent study (Kallen and Olausson, 2007). An alternative explanation is that women with asthma who do not use medication have mild or less severe asthma while those with asthma who use medication are the most severe cases, which may be the real risk. This is supported by Mabie (1996), who says that as asthma severity increases, the number of asthma medications and the frequency of use increase (National Asthma Education and Prevention Program, 1993).

Asthma exacerbations are often marked by shortness of breath, coughing, or wheezing, which may result in interrupted or decreased oxygen supply (hypoxia). Fetal hypoxia can be greater than maternal hypoxia because oxygen dissociation in the fetus is different than in the adult (National Asthma Education and Prevention Program, 1993). Uterine blood flow is also affected by maternal hypoxia as her body will redirect blood to vital organs such as the heart and brain, diverting it away from the uterus (National Asthma Education and Prevention Pro-

gram, 1993). Hypoxia has been shown to cause malformations including distal digital reductions, clefts, and cardiovascular defects in mice and rats (Danielsson, 2003).

This is one of the few studies attempting to look at a specific group of congenital malformations and asthma/asthma medication use. Other studies have only looked at all major defects, which can only result in limited interpretations. In addition, data on congenital malformations in this study were drawn from a statewide registry and cases were confirmed by medical procedure and also reviewed by a pediatric cardiologist. This study also has extensive information available on many potential confounders. One major advantage over other studies is having data on asthma status as well as medication use. This is important information needed to tease apart the effects of disease versus the effects of the medication.

Unfortunately, a major limitation of this study is the lack of information on frequency of medication use or dosage of medication, including whether the medication was inhaled or oral. The relationship between congenital heart defects and asthma medications is difficult to study because of the rarity of both outcome and exposure to any given medication. Therefore, it was necessary to group exposure to medications into very broad categories. We attempted to look at two specific drugs (Ventolin and Theophylline) because these were the two most commonly used, although the numbers are small. We also had no measure of asthma severity, which may have included number of attacks, doctor visits, Pulmonary Function Test results, or other medical records. Thus, we cannot clearly separate the effect of medication from that of asthma. We have attempted to overcome this limitation by using number of asthma medications as a surrogate for severity.

Because this analysis attempted to be more specific than many previous studies with respect to defect and exposure, many of the groups were small and there was little power for some of the presented analyses. However, the group of medication users with asthma had sufficient power and a significant association was found. Furthermore, although some of the results presented here cannot be used to draw conclusions from this study, they may be used for future hypothesis generation because this is one of the first studies to look at this question with this level of detail.

Timing of exposure is another limitation of these data. Women were asked about medication use before pregnancy recognition, after pregnancy recognition to the end of the first trimester, then by second and third trimester. Because heart development is thought to occur between the third and eighth week of gestation (Sadler, 2000), fetal heart development began before pregnancy recognition for many of the women in our study. Women may change their medication use or make different medication decisions based on pregnancy knowledge, which could then affect asthma symptoms and/or heart development of the fetus. However, in this study, most women did not stop their asthma medication use after pregnancy recognition, and some began using medication. Of all women who used medications in the period 1 month before pregnancy to the end of the first trimester, 63% used medications both before and after pregnancy recognition, 12% used medication in the before period only, and 25% began using medication after pregnancy recognition. In addition, conception date is often only an esti-

mate and can be off by 1 week or more. Thus, combining the before and after periods best covers the appropriate exposure period (periconceptional period).

Exposures and confounders were assessed by large blocks of time rather than smaller units because it was felt that using familiar reference points within a pregnancy would aid recall. Because the period used (1 month prior to conception through the end of the first trimester) includes several weeks before the start of heart development and several weeks after the end of heart development, and we did not ask about medication use by week of pregnancy, there may be some misclassification of exposure. However, because asthma is a chronic disease and most women reported medication use during multiple time windows, meaning they used medication multiple times, this proportion may be small. Similarly, assessment of some of the confounders, such as maternal caffeine use, fever, prenatal vitamin use, and trihalomethane exposure, which were measured during the periconceptional period, may be subject to this type of misclassification. Although behaviors may change, caffeine use, vitamin use, and trihalomethane exposure are likely exposures that women experience on a daily basis and, overall, women did not report this exposure differently before and after pregnancy recognition. Therefore, we do not expect that any misclassification within these confounders would greatly influence the results presented.

Because subjects were contacted up to 2 years after the birth of the child, recall bias is a concern. To minimize this bias, a pregnancy calendar was used in conjunction with specific questions, many centered around major milestones of pregnancy. Groups of cases and controls were ascertained and interviewed in the same time period (within the same month), thus, there was no difference between cases and controls with respect to time to interview and any potential recall bias would be nondifferential for this point.

Given the response rate was below 60%, selection bias is a concern. When compared to nonrespondents, those who were interviewed were less likely to live in New York City and less likely to identify themselves as Black or Hispanic. The rates of successful interview within demographic strata were consistently slightly lower among controls, but similar to the total interview rate. Thus, there was little evidence of a differential response rate that might bias the comparisons within the study group between cases and controls. Also, there was no significant difference between the case and control group in the time interval between the birth of the index child and interview. Finally, although these data are older, they were well suited to study this question because of the detailed information collected. Other datasets used to study this question lack information on both medication and disease. Many of the medications used in this study are currently used. For example, the main ingredient in Ventolin, our most commonly used medication, is albuterol, which is still a commonly prescribed asthma medication. In addition, prednisone (an anti-inflammatory) is also still commonly prescribed.

In conclusion, these results suggest that both maternal asthma status (controlled vs. uncontrolled; severe vs. mild) and asthma medication use, particularly bronchodilators, may play a role in cardiac malformations in their offspring. Further studies should examine maternal asthma status and asthma treatment more carefully to

clarify whether the increased risk of cardiac defects is due to maternal asthma severity or maternal asthma medication use.

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