ORIGINAL ARTICLE

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

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ABSTRACT

BACKGROUND

Use of angiotensin-converting–enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. We conducted a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations.

METHODS

We studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and born between 1985 and 2000 for whom there was no evidence of maternal diabetes. We identified 209 infants with exposure to ACE inhibitors in the first trimester alone, 202 infants with exposure to other antihypertensive medications in the first trimester alone, and 29,096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records.

RESULTS

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02).

CONCLUSIONS

Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.

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Angiotensin-converting–enzyme (ACE) inhibitors are effective and generally well tolerated antihypertensive medications.[1,2] However, ACE inhibitors are contraindicated during the second and third trimesters of pregnancy. In utero exposure during this period is associated with ACE-inhibitor fetopathy, a group of conditions that includes oligohydramnios, intrauterine growth retardation, hypocalvaria, renal dysplasia, anuria, renal failure, and death.[3,4]

In contrast, the use of ACE inhibitors in the first trimester of pregnancy has not been linked to adverse birth outcomes. Fetal effects were thought to be the direct consequences of anuria and oligohydramnios resulting from ACE-inhibitor–induced impairment of fetal renal function.[4-6] Because urine production is a gradual process that develops later in pregnancy,[7] the developing fetal kidney was not considered sensitive to ACE-inhibitor effects before the second trimester. Furthermore, ACE inhibitors have not been thought to have teratogenic effects, which usually result from first-trimester exposures. Although some congenital malformations, such as skull-ossification defects and patent ductus arteriosus, have been reported in conjunction with the use of ACE inhibitors, these have been explained as the secondary effects of fetal renal impairment.[4-6]

The evidence that first-trimester exposure to ACE inhibitors does not cause congenital malformations comes from a limited number of studies in animals and analyses of case reports. Data on fetal outcomes in humans are limited to several small, uncontrolled series and unpublished reports.[3,8-12] However, because angiotensin II receptors are widely expressed in fetal tissue and could have an important role in fetal development,[13,14] it is possible that first-trimester exposure to ACE inhibitors increases the risk of congenital malformations. To clarify the safety of the use of ACE inhibitors during pregnancy, we used a large Medicaid database to conduct an epidemiologic study assessing the association between exposure to ACE inhibitors during the first trimester of pregnancy and the risk of congenital malformations.

METHODS

SOURCES OF DATA AND BIRTHS STUDIED

The study was based on Tennessee Medicaid data, which provide a good record of maternal medication use from computerized records of filled prescriptions. Links to files of vital records (birth, death, and fetal-death certificates)[15] and to medical records permit identification of pregnant women, estimation of conception dates, and identification of potential congenital malformations.[16,17] Vital records, Medicaid enrollment records, and linked U.S. Census data[18] provided information on maternal and infant factors, including age, maternal race (from self-report on the birth certificate), education, prior pregnancies, county of residence, median neighborhood (census-block group) income, late entry into prenatal care (after the fourth month of pregnancy),[19] smoking during pregnancy, year of the child's birth, and multiple births. The date of the last menstrual period was obtained from the birth certificate if the date was available (89.3 percent of all births) or estimated from birth weight according to the race- and calendar-year–specific distributions of gestational age for births to mothers for whom the date of the last menstrual period was known.[20] Of the mothers and infants for whom medical records were reviewed, 93.6 percent had the last menstrual period of the mother recorded within two weeks before or after the date estimated by this procedure.

Maternal use of prescribed medications was determined from Medicaid pharmacy files, which included the date when the prescription was filled and the number of days for which the medication was supplied. Computerized pharmacy records have been shown to be an accurate source of medication data[15] and have high rates of concordance with self-reports of medication use by patients.[15,21,22] Diagnoses based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) from Medicaid inpatient, emergency department, and physician-visit records were used to identify chronic maternal illnesses as well as potential congenital malformations.

The first trimester was defined as the first day of the last menstrual period and the subsequent 90 days; prescription of medication with directions for use beyond this period was considered to indicate exposure later in pregnancy. A fetus was considered to have been exposed to a medication during a given trimester if the medication had been prescribed to the mother to be taken on at least one day during the trimester.

Infants (including live births and fetal deaths) in the present study were identified in conjunc-

tion with another study of antimicrobial agents and congenital malformations. The potential study population included infants born between 1985 and 2000 with maternal enrollment in Medicaid throughout pregnancy, with complete birth-certificate information for key variables (99.9 percent of potential cohort births), and with enrollment for the first 90 days of life or through the date of death (90.1 percent of births). From this population, we identified 33,810 infants who were eligible for the antimicrobial study, were in a randomly sampled control group with no maternal use of antimicrobial agents, or had had fetal exposure to ACE inhibitors.

Because diabetes is strongly associated with congenital malformations[23,24] and because ACE inhibitors are frequently prescribed to patients with diabetes, we restricted the study to infants whose mothers had no evidence of diabetes before or during pregnancy. Evidence of diabetes was defined by two or more prescriptions for insulin or oral hypoglycemic agents, an outpatient diagnosis of diabetes with at least one prescription for insulin or an oral hypoglycemic agent, or any hospital-discharge diagnosis of diabetes. A total of 32,749 infants remained after exclusion of those whose mothers had evidence of diabetes. We also excluded 2 infants whose mothers were prescribed angiotensin-receptor antagonists (which may have fetal effects similar to those of ACE inhibitors[25]), 1001 infants who were exposed to ACE inhibitors or other antihypertensive medications beyond the first trimester, and 2239 infants with fetal exposure to other potential teratogens (androgens, warfarin, anticonvulsants, lithium, streptomycin, kanamycin, fluconazole, tetracycline, methylprednisolone, prednisone, estrogens, misoprostol, thalidomide, iodine, methimazole, carbimazole, isotretinoin, statins, quinine, ribavirin, chenodiol, live vaccines, aminopterin, or clomiphene), leaving 29,507 infants in the study.

MAJOR CONGENITAL MALFORMATIONS

The study outcome was the presence of a major congenital malformation not related to a chromosomal defect or a clinical genetic syndrome. Potential cases were identified from multiple sources, including the birth certificate checkbox (from 1989 on), infant hospitalization records (birth to day 365 of life), fetal death certificates (after 20 weeks of gestation) or infant death certificates (before the first birthday), and maternal hospitalization records (for delivery or fetal death). For multiple births in which one infant was a potential case patient, the associated twin or triplets were also considered as potential case patients.

For each potential case of congenital malformation, trained study nurses who were unaware of the maternal status of drug exposure reviewed the pertinent medical records of the mothers and infants to complete a structured abstract form. The reviewers confirmed demographic information and recorded any congenital malformations and malformation-specific confirmatory data included in the face sheet, discharge summary, birth record, admission history, physical examination, reports of surgical procedures, imaging studies, autopsy records, or transfer hospitalization records. Confirmed cases met the definitions of major congenital malformations used by the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program.[26] This program has conducted surveillance for birth defects since 1967, and its definitions have been validated in several previous studies.[27] These criteria include more detail than classifications based on ICD-9-CM codes alone and use case-ascertainment methods very similar to those of our study. They also consider gestational age; for example, infants classified as having patent ductus arteriosus had to have a gestational age of more than 36 weeks.[26] The principal investigator, who was unaware of the mother's drug-exposure status, assigned each infant a final diagnosis from the CDC code-book index.[26] If the diagnosis was ambiguous, it was adjudicated with a second investigator. Potential cases for which the medical record mentioned the diagnosis but the necessary supporting data were absent were not considered confirmed malformations.

STATISTICAL ANALYSIS

All study infants were classified according to maternal use of ACE inhibitors in the first trimester only. Because treated hypertension, the indication for ACE inhibitors, was a potential confounder, we also identified infants who had exposure to other antihypertensive medications only during the first trimester (excluding beta-blockers and calcium-channel blockers prescribed only for migraine; diuretics prescribed only for heart failure or peripheral edema; and beta-blockers and calcium-channel blockers prescribed only for arrhythmia) during the first trimester alone. This

classification resulted in three mutually exclusive categories defined according to maternal use of antihypertensive agents: ACE inhibitors in the first trimester only, other antihypertensive agents in the first trimester only, or no antihypertensive agents throughout pregnancy.

The study outcome was the proportion of infants in each of the three exposure categories with any major congenital malformation. Malformations of systems arising from the same embryonic origin[7] were grouped together a priori according to the CDC criteria. Except when otherwise noted, infants with multiple malformations were included in the analyses for each of the individual malformations.

Risk ratios were calculated with the use of the group with no in utero exposure to antihypertensive medications as the reference category. The risk ratios were adjusted for potential confounders by modified Poisson regression[28,29] that accounted for the possible correlation induced by multiple gestations and pregnancies with the use of generalized estimating equations.[30] The final model included the year of the child's birth and maternal race, age, rural as compared with urban residence, quartile of neighborhood income, and the presence or absence of chronic illness (epilepsy, sickle cell disease, asthma, renal disease, neoplastic disease, cardiovascular disease [other than hypertension or diabetes], human immunodeficiency virus infection, cystic fibrosis, autoimmune diseases, cerebrovascular diseases, mental illness, obesity, migraine headaches, Crohn's disease, ulcerative colitis, and organ transplantation). Controlling for maternal antibiotic exposure and other potential confounders (maternal education and smoking) did not substantially affect the study findings. In some analyses, the proportions of infants with congenital malformations, adjusted for potential confounders, were estimated by the method of marginal prediction.[31]

Permission to perform the study and waiver of the need for informed consent were obtained from the Vanderbilt University institutional review board, the Tennessee Health Department, the TennCare Bureau, and the hospitals where medical records were reviewed.

RESULTS

The 29,507 study births included 411 infants who were exposed to antihypertensive medications in the first trimester alone. In comparison with the mothers of the 29,096 infants with no such exposure, the mothers of these infants were older and had more education; were more likely to be multigravid, live in rural counties, and have one or more chronic illnesses; and were less likely to have had late prenatal care (Table 1).

Of the 411 infants, 209 had been exposed to ACE inhibitors only in the first trimester and 202 to other antihypertensive medications only in the first trimester. The characteristics of the mothers of these two groups of infants were generally similar, although the mothers of the infants exposed to ACE inhibitors were slightly older and had more education. The proportion of infants born in level III neonatal facilities (those providing tertiary care, with complete perinatal services) was nearly identical in the three groups (about 40 percent).

Major congenital malformations were diagnosed in 856 infants (2.9 percent); 203 had more than one malformation. There were 305 infants with cardiovascular malformations (including 141 with atrial septal defect, 124 with patent ductus arteriosus, 76 with ventricular septal defect, and 29 with pulmonic stenosis), 195 with musculoskeletal malformations (including 136 with polydactyly, 20 with upper-limb defects, and 10 with craniofacial anomalies), 119 with gastrointestinal malformations (including 62 with pyloric stenosis and 20 with intestinal atresias), 83 with central nervous system malformations (including 24 with hydrocephalus, 17 with microcephaly, 9 with spina bifida, and 2 with encephalocele), 87 with genital malformations, and 82 with urologic malformations (including 28 with renal malformations).

Among infants with exposure to ACE inhibitors in the first trimester alone, the adjusted proportion with any major congenital malformation was 7.1 percent (Table 2). In comparison with children with no fetal exposure to antihypertensive medications, the risk of major congenital malformations in this group was increased by a factor of more than 2 (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27). The increased risk was due primarily to increased risks of malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02). The risk of all other types of malformations was

Table 1. Distribution of Maternal Characteristics According to the Presence or Absence of Fetal Exposure to Antihypertensive Medications during the First Trimester Alone.

Characteristic	ACE Inhibitor (N=209)	Other Antihypertensive Medication (N=202)	No Antihypertensive Medication (N=29,096)*
Mean maternal age at delivery (yr)	28.3†	25.3	22.4‡
	% of infants with specified maternal characteristic		
Black race§	46.9	43.6	48.6
Education ≥12 yr	73.1†	55.0	50.2‡
Primigravida	12.0	15.8	24.1‡
Rural residence¶	36.4	35.2	30.3‡
Lowest income quartile	19.6	23.8	25.5
Any chronic illness‖	29.7	30.7	13.4‡
Cardiovascular disease other than hypertension	6.7	7.4	1.4‡
Mental illness	11.5	12.4	5.2‡
Asthma	2.4†	6.4	2.8
Late prenatal care**	6.7	7.9	12.4‡
Smoking during pregnancy	32.0	28.3	29.1
Delivery in a level III facility	40.2	38.6	39.8

* Mothers of infants in this group took no antihypertensive medications throughout pregnancy.
† P<0.05 for the comparison with the group exposed to other antihypertensive medications.
‡ P<0.05 for the comparison with the other two groups.
§ Maternal race was reported by the mother on the birth certificate.
¶ Rural residence is defined as residence outside a standard metropolitan statistical area.
‖ Chronic illnesses are defined as epilepsy, sickle cell disease, asthma, renal disease, neoplastic disease, cardiovascular disease, human immunodeficiency virus infection, cystic fibrosis, autoimmune diseases, cerebrovascular disease, chronic mental illness, obesity, migraine headaches, Crohn's disease, ulcerative colitis, and organ transplantation. Hypertension and diabetes are not included.
** Late prenatal care is defined as care beginning some time after the fourth month of pregnancy.

not significantly increased (risk ratio, 1.75; 95 percent confidence interval, 0.79 to 3.89), although a post hoc analysis found an increased risk of renal malformations (risk ratio, 9.32; 95 percent confidence interval, 1.79 to 48.5) as compared with children with no fetal exposure. In contrast, the risks of any major congenital malformation and of the specific types of malformations were not increased in infants with exposure to other antihypertensive medications during the first trimester alone, as compared with those with no fetal exposure to any hypertensive medications (Table 2).

Table 3 describes the characteristics of the 18 infants exposed to ACE inhibitors in the first trimester alone who had major congenital malformations. Seven had multiple malformations. The mother's age ranged from 17 to 41 years, and the infant's gestational age at delivery ranged from 32 to 41 weeks; 17 were single births. According to records of prescriptions filled, all but three of these infants had been exposed to ACE inhibitors during at least two months of the first trimester. In eight of the nine infants with cardiac malformations, the medical record documented confirmation of the diagnosis by an echocardiogram or other test.

To test the robustness of study definitions, we conducted several secondary analyses (Table 4). These included restricting the group exposed to ACE inhibitors to infants whose mothers filled a prescription for ACE inhibitors 14 or more days after the last menstrual period (thus excluding women who were likely to have stopped use of ACE inhibitors before conception was likely to have occurred), using a broader definition of diabetes (further excluding women with a single prescription for a hypoglycemic agent or one outpa-

Table 2. Risk of Major Congenital Malformations among Study Infants According to Fetal Exposure to Antihypertensive Medications during the First Trimester Alone.*

Variable	ACE Inhibitor (N=209)	Other Antihypertensive Medication (N=202)	No Antihypertensive Medication (N=29,096)†
Any congenital malformation			
No. of infants	18	4	834
Percentage of births	7.12	1.73	2.63
Risk ratio	2.71	0.66	1
95% confidence interval	1.72–4.27	0.25–1.75	Reference
Cardiovascular malformation			
No. of infants	9	2	294
Percentage of births	2.90	0.70	0.78
Risk ratio	3.72	0.89	1
95% confidence interval	1.89–7.30	0.22–3.59	Reference
Central nervous system malformation			
No. of infants	3	0	80
Percentage of births	1.46	0	0.33
Risk ratio	4.39	—	1
95% confidence interval	1.37–14.02	—	Reference
Other malformations			
No. of infants	6	2	469
Percentage of births	2.71	0.95	1.55
Risk ratio	1.75	0.62	1
95% confidence interval	0.79–3.89	0.15–2.45	Reference

* Infants could have both cardiovascular and central nervous system malformations and be included in these groups; the other malformations group included only infants without cardiovascular or central nervous system malformations. The proportions and risk ratios are adjusted for potential confounders. Models include maternal age, race, presence or absence of a chronic illness, rural or urban residence, and income quartile and the year of the child's birth. The estimation accounts for clustering due to a woman with either multiple pregnancies during the study period or a multiple-gestation pregnancy.

† Infants in this group had no fetal exposure to antihypertensive medications.

tient visit with a diabetes diagnosis through the first trimester, who were not considered to have diabetes according to our original definition), and excluding patent ductus arteriosus as a major congenital malformation (since this condition infrequently persists for more than a few days after birth in term infants). The statistically increased risks of any malformation, cardiovascular malformations, and central nervous system malformations conferred by exposure to ACE inhibitors remained (Table 4).

DISCUSSION

In this epidemiologic study, we found that fetal exposure to ACE inhibitors restricted to the first trimester of pregnancy, an exposure that was previously considered to be safe,[4,8-10] was associated with a risk of a major congenital malformation that was 2.7 times as great as the risk with no fetal exposure to ACE inhibitors or other antihypertensive medications. Prespecified subgroup analyses identified significantly increased risks of malformations of the cardiovascular and central nervous systems. In a post hoc analysis, we also found a significantly increased risk of kidney malformations, although the numbers were small and the 95 percent confidence intervals were wide.

We consider it unlikely that the observed associations are due to confounding by factors associated with the use of ACE inhibitors. Because diabetes is an indication for the use of ACE in-

Table 3. Characteristics of Infants Born with Major Malformations after Fetal Exposure to ACE Inhibitors during the First Trimester Alone.

Malformation	Maternal Age	Gestational Age	Multiple or Single Birth	Months of 1st-Trimester Exposure	Age at 1st Diagnosis	Age at Last Diagnosis during 1st Yr of Life	Diagnostic Confirmation
	yr	*wk*			*days*		
Atrial septal defect, pulmonic stenosis	28	32	Triplet	1, 2	5	15	Repeated echocardiography
Atrial septal defect, pulmonic stenosis, patent ductus arteriosus	40	38	Singleton	1, 2, 3	0	18	Cardiac catheterization
Atrial and ventricular septal defects, pulmonic stenosis	18	40	Singleton	1, 2, 3	0	187	Cardiac catheterization
Atrial septal defect, patent ductus arteriosus	19	37	Singleton	1	0	227	Repeated echocardiography
Atrial septal defect, patent ductus arteriosus	20	40	Singleton	1	1	14	Repeated echocardiography
Atrial septal defect	26	36	Singleton	1, 2, 3	0	8	Repeated echocardiography
Patent ductus arteriosus	17	38	Singleton	2, 3	1	3	Repeated echocardiography
Patent ductus arteriosus	28	41	Singleton	1, 2, 3	3	3	Echocardiography
Ventricular septal defect	21	41	Singleton	1, 2, 3	4	354	Evaluation by pediatric cardiologist
Spina bifida	31	35	Singleton	1, 2	0	10	Neurosurgical repair
Microcephaly, eye anomaly	24	39	Singleton	1, 2	0	212	Evaluation by pediatric ophthalmologist
Coloboma	33	37	Singleton	1, 2, 3	4	267	Evaluation by pediatric ophthalmologist
Renal dysplasia	32	37	Singleton	1, 2, 3	3	341	Ultrasonography
Renal dysplasia	21	39	Singleton	1, 2	1	192	Evaluation by urologist
Hypospadias	34	37	Singleton	1	0	2	Evaluation by urologist
Intestinal atresia, choanal atresia	36	35	Singleton	1, 2, 3	0	7	Transfer for surgery
Hirschsprung's disease	27	40	Singleton	1, 2, 3	2	209	Surgical repair
Diaphragmatic hernia	41	38	Singleton	1, 2, 3	0	112	Surgical repair

hibitors and is also strongly associated with an increased risk of congenital malformations,[23,24] we excluded women with known diabetes. Hypertension itself has not been associated with congenital malformations.[32] However, to assess the potential for direct or indirect confounding by this factor, we identified infants whose mothers had used other antihypertensive medications during the first trimester of pregnancy. The absence of an increased risk of major congenital malformations in this group is evidence that hypertension is also unlikely to be a confounder, although we cannot rule out confounding by other factors, such as the severity of hypertension.

The potential limitations of our definition of first-trimester exposure to ACE inhibitors should be recognized. Some of the exposures may have occurred before conception. However, the findings were not substantially changed in a secondary analysis that used a definition that required the mother to have filled a prescription for ACE inhibitors at least 14 days after the last menstrual period. We determined medication exposure from filled prescriptions, an approach that would not identify women who stopped taking the medication on learning they were pregnant. However, the resultant misclassification would attenuate the observed association of ACE inhibitors and

Table 4. Alternative Analyses of Risk of Major Congenital Malformations among Study Infants with Fetal Exposure to ACE Inhibitors during the First Trimester Alone.*

Alternative Analysis	Any Malformation		Cardiovascular Malformation		Central Nervous System Malformation	
	Risk Ratio (95 Percent Confidence Interval)					
Entire study group	2.71	1.72–4.27	3.72	1.89–7.30	4.39	1.37–14.02
ACE inhibitor prescription filled >14 days after last menstrual period	2.96	1.83–4.79	4.04	1.98–8.25	5.45	1.69–17.64
Broader definition of diabetes†	2.77	1.76–4.37	3.81	1.94–7.49	4.48	1.40–14.38
Patent ductus arteriosus excluded	2.51	1.54–4.09	3.35	1.55–7.27	4.39	1.37–14.02

* The reference category is infants with no fetal exposure to any antihypertensive medication. The risk ratio is adjusted for potential confounders. Models include maternal age, race, presence or absence of a chronic illness, rural or urban residence, income quartile, and the year of the child's birth. The estimation accounts for clustering due to multiple pregnancies and twins or triplets.

† The broader definition also excludes infants whose mothers had only a single hypoglycemic prescription or one outpatient visit with a diagnosis of diabetes through the first trimester. These women were not considered to have diabetes according to our original definition.

congenital malformations and thus cannot explain our findings.

We used the CDC definitions of major congenital malformations, which include patent ductus arteriosus in infants born after at least 36 weeks of gestation. Although a patent ductus arteriosus does not usually persist in term infants, it is present at birth infrequently and may resolve spontaneously without long-term sequelae. However, in a secondary analysis excluding infants with patent ductus arteriosus, the association between the use of ACE inhibitors and cardiovascular malformations remained significant. Other cardiovascular malformations may be detected by echocardiography in asymptomatic infants; bias could occur if there were increased surveillance of infants who were exposed in utero to ACE inhibitors. However, the proportion of infants born in level III neonatal facilities, where echocardiography is most likely to be performed, did not vary according to exposure to antihypertensive medications.

Our results are consistent with other data that suggest that inhibition of the renin–angiotensin system with ACE inhibitors early in pregnancy could affect fetal organ development. Several studies have shown that the expression of the type 2 angiotensin receptor peaks early in gestation and then gradually declines.[13,14] Angiotensin II has a role in the early embryologic development of the heart, kidney, and brain.[13,14] Mice with an abnormality in chromosome 3q, on which the gene for the angiotensin receptor resides, have increased rates of ventricular septal defects,[33] an observation suggesting a possible ontogenic role of the angiotensin receptor in the formation of the ventricular septum. ACE inhibitors also have been shown to inhibit the proliferation of fetal smooth-muscle cells in the ductus arteriosus, which might lead to patent ductus arteriosus.[14] Our findings are based on small numbers, however, and should be confirmed in other studies that address possible mechanisms for teratogenicity of ACE inhibitors as well as the effects of specific drugs, doses, and durations.

As indications for ACE inhibitors have expanded,[2,34] their use among women of childbearing age has increased. Data from the National Ambulatory Medical Care Survey show that between 1995 and 2002 the use of ACE inhibitors in female patients 15 through 44 years of age increased by 83 percent (from 2.4 percent to 4.4 percent).[35] This increase in use is likely to result in an increase in first-trimester fetal exposures. Our data suggest that such exposures cannot be considered safe and should be avoided.

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