Infant and Maternal Outcomes in the Pregnancies of Asthmatic Women

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We examined the relationship between infant and maternal outcomes and asthma complicating pregnancy, using historical cohort analysis of singleton live deliveries in New Jersey hospitals between 1989 and 1992 (n = 447,963). Subject mother-infant dyads were identified from linked birth certificate and maternal and newborn hospital claims data. Women with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code (493) for asthma (n = 2,289) were compared with a fourfold larger randomly selected control sample (n = 9,156) from the remaining pool of women. After controlling for the effects of important confounding variables, maternal asthma was associated with the following adverse infant outcomes: preterm infant (odds ratio [OR] = 1.36; 95% confidence interval [CI], 1.18 to 1.55), low birth weight (OR = 1.32; 95% CI, 1.10 to 1.58), small-for-gestational age (OR = 1.26; 95% CI, 1.10 to 1.45), congenital anomalies (OR = 1.37; 95% CI, 1.12 to 1.68), and increased infant hospital length of stay (OR = 1.44; 95% CI, 1.25 to 1.65). The adverse maternal outcomes associated with maternal asthma were: pre-eclampsia (OR = 2.18; 95% CI, 1.68 to 2.83), placenta previa (OR = 1.71; 95% CI, 1.05 to 2.79), cesarean delivery (OR = 1.62; 95% CI, 1.46 to 1.80), and increased maternal hospital length of stay (OR = 1.86; 95% CI, 1.60 to 2.15). The results emphasize the need for maternal asthma to be added to the list of conditions that increase the risk of adverse pregnancy outcomes. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women.

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Asthma is the most frequent respiratory disorder complicating pregnancy, affecting between 0.4 and 1.3% of pregnant women (1, 2). Because of its increasing frequency in the general population, asthma is becoming a more prominent medical problem for both children and adults. Despite considerable research on the causes and treatment of this condition, there has been relatively little attention given to the growing problem of asthma in pregnancy. We have had an opportunity to examine this issue among women delivering singleton births in a large and representative population. We have reported elsewhere that the newborns of asthmatic women have an increased incidence of transient tachypnea (3), and we have now examined several other pregnancy outcomes in the same large population of asthmatic women.

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METHODS

Design and Subject Selection

The methods for this historical cohort study have been described elsewhere (3). The data were obtained from an administrative data base that contains linked birth certificate, infant death certificate, and maternal and newborn hospital discharge claims data for the delivery hospitalization for all singleton, live births to in-state residents in New Jersey hospitals between 1989 and 1992 (n = 447,963). The match rate for the database was 94.5% of these births for 1989, 95.3% for 1990, 95.5% for 1991, and 95.8% for 1992. Emergency room visits and hospitalization for asthma are not included in this database.

From these linked data in each calendar year (1989 to 1992), mothers with an International Classification of Diseases, Ninth Revision (ICD-9-CM) diagnosis code of 493 (asthma) in any of the nine diagnosis fields were first selected (n = 391 for 1989, n = 540 for 1990, n = 647 for 1991, and n = 711 for 1992). For each year, a control sample that was four times larger than the count of cases was then selected randomly from the remaining pool of mothers. Cases from the four years (n = 2,289) were combined and compared with the combined control subjects (n = 9,156) with respect to adverse infant and maternal outcomes.

Infant Outcomes

Birthweight and gestational age were obtained from the birth certificate. The accuracy of gestational age recorded on the birth certificate has been questioned (4), but estimates based on the last menstrual period appear to be reasonably satisfactory (5, 6). Balcazar (7) found that the greatest degree of error in reporting was at the extremes of the distribution. To reduce error caused by misreporting of gesta-

tional age, we limited the analysis to infants in the 22- to 45-wk range, resulting in the removal of 35 (1.53%) cases and 240 (2.62%) control mothers from analyses involving this variable.

For a measure of newborn size in relation to gestational age, we used the fetal growth ratio because it conveys information about the degree of underweight or overweight relative to internally derived means. It is calculated as the quotient of the observed birth weight divided by the mean birth weight for gestational age (week by week) of a sex- and race/ethnicity-specific fetal growth distribution (8–10). The cutoff points of small-for-gestational age and large-for-gestational age have been validated by other investigators (9, 11).

Very low birth weight was defined as birth weight $< 1{,}500$ g; low birth weight as birth weight $< 2{,}500$ g; high birth weight as birth weight $> 4{,}000$ g; preterm birth as gestational age < 37 completed weeks; postterm birth as gestational age ≥ 42 wk; very-small-for-gestational age as a fetal growth ratio < 0.75; small-for-gestational age as a fetal growth ratio < 0.85; and large-for-gestational age as a fetal growth ratio > 1.15.

Congenital anomalies can be separated into those that represent a single primary defect in development and those that represent a multiple malformation syndrome (12). Single primary defects are etiologically heterogenous and mostly have presumed environmental etiology. Multiple malformation syndrome is used when several observed structural defects all have the same known or presumed etiology, such as chromosomal abnormalities, teratogens, or single-gene defects inherited in Mendelian patterns. Single primary defects in development can be further subcategorized into malformation (arising from a localized error in morphogenesis), deformation (alteration in shape or structure of a part that has differentiated normally), and disruption (destruction of a previously, normally formed part). Because asthma severity usually increases between 29 and 36 wk of gestation (13), we hypothesized a priori that maternal asthma might be associated with deformations and not with malformations. For this analysis, we defined three groups of congenital anomalies using ICD-9-CM diagnosis codes: deformations, nondeformation congenital anomalies, and all congenital anomalies (ICD-9-CM codes for these subgroups are available on request).

Maternal Outcomes

Maternal complications were defined using the ICD-9-CM diagnosis and procedure codes as follows.

Preterm labor. Idiopathic preterm labor (those women with preterm labor = 644.2, excluding those with uterine malformations = 654.0, known uterine tumors = 654.1, cervical incompetence = 654.5, placenta previa = 641.0 to 641.1, premature separation of placenta = 641.2, type I or insulin-dependent diabetes mellitus = 250.0 to 250.9 with a fifth digit code of 1, type II or noninsulin-dependent diabetes mellitus = 250.0 to 250.9 with a fifth digit code of 0, gestational diabetes = 648.0, preexisting hypertension = 401.0 to 405.0 and 642.0 to 642.2, polyhydramnios = 657.0, or medical or surgical induction of labor = ICD-9-CM procedure code = 730 to 734); early idiopathic preterm labor (idiopathic preterm labor further restricted to those pregnancies with 34 or less completed weeks of gestation). The newborn's gestational age from the birth certificate was used to define this variable.

Hypertensive disorders of pregnancy. Pre-eclampsia (642.4 to 642.5); transient hypertension of pregnancy (642.3); pregnancy-induced hypertension (defined as either of pre-eclampsia, transient hypertension of pregnancy, pre-eclampsia superimposed on preexisting hypertension, or unspecified hypertension of pregnancy = 642.3 to 642.9).

Antepartum hemorrhage. Placenta previa (641.0 to 641.1); premature separation of placenta (641.2).

Membrane-related disorders. Premature rupture of membranes (658.1); infection of the amniotic cavity (658.4).

Mode of delivery. Forceps (ICD-9-CM procedure code, 72.0 to 72.4); vacuum (ICD-9-CM procedure code, 72.7); cesarean (ICD-9-CM procedure code, 74.0).

Others. Postpartum hemorrhage (666.0 to 666.2); the variable length of hospital stay is available in the claims data.

Other Patient Characteristics

Adequacy of prenatal care was defined using the index developed by Kotelchuck (14). This index considers both adequacy of initiation of prenatal care and adequacy of service utilization once care has begun, and it characterizes prenatal care as none, inadequate, intermediate, adequate, and intensive (or adequate plus) care. Variables used to create this index were obtained from the birth certificate. The mother's age, race/ethnicity, level of education, marital status, parity, cigarette smoking, and alcohol use were also derived from the birth certificate.

Information on payer (insurance type) was obtained from the mother's primary insurance coded on the hospital Unified Billing Patient Summary at the time of delivery. The ICD-9-CM diagnosis codes 304 and 648.3 from this summary were used to define illicit drug use in pregnancy.

Statistical Analysis

Infant and maternal adverse outcomes were the dependent variables. Maternal asthma as coded in the record of the delivery hospitalization was the explanatory variable of interest.

Adverse infant and maternal outcomes were analyzed in relation to maternal asthma using unconditional multiple logistic regression before and after accounting for potential confounding variables (15). For each outcome, a separate regression model was constructed, including maternal asthma as an explanatory variable. Selection and order of entry of confounding variables for each model were determined using a priori knowledge according to the method described by Greenland (16). Statistical significance of regression coefficients was determined by the chi-square approximation to the likelihood ratio statistic and was defined as a two-tailed $p < 0.05$. Analysis was carried out using SAS statistical software.

RESULTS

The characteristics of the overall study population of 447, 963 singleton live births have been reported elsewhere (3), and are typical of industrialized states in the United States. Approximately 15% of the mothers had less than a high school education and about 22% had a government assistance program as their primary source of medical insurance. Forty-four percent of the births were to primiparous mothers. About two-thirds of the mothers received adequate or more than adequate prenatal care. The overall prevalence of a discharge diagnosis of asthma among these New Jersey mothers was 0.5%.

Characteristics of the 2,289 asthmatic mothers and the sample of 9,156 nonasthmatic control mothers included in the present analyses have been detailed elsewhere (3). The characteristics on which asthmatic mothers had higher percentages than control mothers (age younger than 20, less than a high school education, currently unmarried, African-American or Hispanic, less than adequate prenatal care, smoking, diabetes, and pre-existing hypertension) were considered potential confounders needing to be controlled in the analyses of pregnancy outcomes reported below.

The frequencies of each of the maternal and infant outcomes for which models were constructed to test association with maternal asthma are reported in Table 1. The asthmatic women appear more likely to have preterm labor and to deliver their infants before 37 wk of gestation. Their babies also tended to weigh less than the infants of nonasthmatic women delivered at the same gestational age. Congenital anomalies were slightly more common in the babies of the asthmatic women. Hypertensive disorders of pregnancy were twice as likely among asthmatic women. The asthmatics were also more likely than other women to be delivered by cesarean section and to have prolonged hospital stays.

Separate logistic regression models, constructed for the different infant and maternal outcomes, confirmed that, for the infants, maternal asthma was statistically associated with low birth weight and with very low birth weight (Table 2). Associations with pre-term delivery, small-for-gestational age, very-small-for-gestational age, congenital anomalies, and infant

TABLE 1

FREQUENCIES OF INFANT AND MATERNAL OUTCOMES IN PREGNANCIES OF ASTHMATIC AND CONTROL MOTHERS

	Asthmatic Mothers (*n = 2,289*)	Control Mothers (*n = 9,156*)
Delivery, %		
Preterm infant	18.0	12.1
Post-term infant	4.7	4.3
Birth weight, %		
Very low	1.7	1.2
Low	9.3	6.1
High	9.5	11.0
Fetal growth, %		
Very small for gestational age	4.2	2.8
Small for gestational age	15.1	11.8
Large for gestational age	12.4	12.5
Congenital anomalies, %		
Deformations	2.2	1.8
Anomalies other than deformations	4.5	3.4
Any	6.4	4.9
Infant hospital length of stay > 3 d, %	44.7	31.7
Preterm labor, %		
Idiopathic preterm labor	7.1	4.2
Early idiopathic preterm labor	3.1	1.8
Hypertensive disorders of pregnancy, %		
Pre-eclampsia	4.5	2.1
Transient hypertension of pregnancy	2.8	1.5
Pregnancy-induced hypertension	7.9	3.9
Antepartum hemorrhage, %		
Placenta previa	1.1	0.7
Premature separation of placenta	1.0	0.8
Membrane disorders, %		
Premature rupture of membranes	6.6	6.1
Infection of the amniotic cavity	1.7	1.6
Mode of delivery, %		
Forceps	5.1	5.4
Vacuum	2.8	3.8
Cesarean	35.9	24.9
Other, %		
Postpartum hemorrhage	1.3	1.4
Maternal hospital length of stay > 3 d	47.0	32.3

TABLE 2

ASSOCIATIONS OF ADVERSE INFANT OUTCOMES AND MATERNAL ASTHMA

	Odds Ratio for Maternal Asthma (95% Confidence Interval)	
	Unadjusted	Adjusted
Delivery		
Preterm infant	1.59 (1.40–1.80)	1.36 (1.18–1.55)†
Post-term infant	1.11 (0.89–1.38)	1.18 (0.94–1.49)*
Birth weight		
Very low	1.48 (1.02–2.13)	1.29 (0.87–1.92)§
Low	1.57 (1.34–1.86)	1.32 (1.10–1.58)§
High	0.86 (0.73–1.00)	0.92 (0.78–1.08)*
Fetal growth		
Very small for gestational age	1.52 (1.20–1.93)	1.36 (1.05–1.76)‡
Small for gestational age	1.33 (1.17–1.51)	1.26 (1.10–1.45)‡
Large for gestational age	0.99 (0.86–1.14)	0.94 (0.81–1.09)‡
Congenital anomalies		
Deformations	1.24 (0.90–1.71)	1.34 (0.97–1.86)*
Anomalies other than deformations	1.34 (1.07–1.69)	1.38 (1.09–1.76)*
Any	1.32 (1.09–1.60)	1.37 (1.12–1.68)*
Infant hospital length of stay > 3 d	1.74 (1.58–1.91)	1.44 (1.25–1.65)¶

* Adjusted for the effects of maternal age, maternal education, marital status, parity, race/ethnicity, diabetes (type I, type II, and gestational), preexisting hypertension, cigarette smoking, and substance and alcohol use during pregnancy.

† Adjusted for * plus for the effects of placenta previa, premature separation of placenta, incompetent cervix, congenital anomalies of the uterus, uterine tumor, cesarean delivery, and medical and surgical induction of labor.

‡ Adjusted for * excluding race/ethnicity.

§ Adjusted for * plus cesarean delivery.

¶ Adjusted for maternal age, maternal education, parity, race/ethnicity, preterm infant congenital anomalies, very small for gestational age, and cesarean delivery of mother.

TABLE 3

ASSOCIATIONS OF ADVERSE MATERNAL OUTCOMES AND MATERNAL ASTHMA

	Odds Ratio For Maternal Asthma (95% Confidence Interval)	
	Unadjusted	Adjusted
Preterm labor		
Idiopathic preterm labor	1.73 (1.43–2.09)	1.53 (1.25–1.87)*
Early idiopathic preterm labor	1.77 (1.34–2.34)	1.51 (1.11–2.04)*
Hypertensive disorders of pregnancy		
Pre-eclampsia	2.20 (1.72–2.81)	2.18 (1.68–2.83)†
Transient hypertension of pregnancy	1.94 (1.44–2.61)	1.94 (1.41–2.65)†
Pregnancy-induced hypertension	2.10 (1.74–2.52)	2.09 (1.72–2.55)†
Antepartum hemorrhage		
Placenta previa	1.74 (1.10–2.77)	1.71 (1.05–2.79)‡
Premature separation of placenta	1.16 (0.72–1.87)	1.08 (0.64–1.81)†
Membrane disorders		
Premature rupture of membranes	1.09 (0.90–1.31)	1.10 (0.90–1.34)†
Infection of the amniotic cavity	1.11 (0.78–1.59)	1.07 (0.73–1.55)†
Mode of delivery		
Forceps	0.95 (0.77–1.17)	0.95 (0.77–1.17)
Vacuum	0.73 (0.56–0.96)	0.73 (0.55–0.95)
Cesarean	1.69 (1.54–1.87)	1.62 (1.46–1.80)§
Other		
Postpartum hemorrhage	0.93 (0.62–1.39)	0.95 (0.63–1.44)¶
Hospital length of stay > 3 d	1.86 (1.70–2.04)	1.86 (1.60–2.15)‖

* Adjusted for the effects of maternal age, maternal education, marital status, parity, race/ethnicity, cigarette smoking, and substance and alcohol use during pregnancy.

† Adjusted for * plus for the effects of diabetes (type I, type II, and gestational) and preexisting hypertension.

‡ Adjusted for * plus for the effect of previous cesarean section.

¶ Adjusted for * plus for the effects of coagulation disorders and uterine tumor.

§ Adjusted for the effects of diabetes mellitus, preterm infant, placenta previa, preeclampsia, and breech presentation.

‖ Adjusted for * plus for the effects of cesarean delivery and postpartum hemorrhage.

hospital stay of more than three days (the median stay) were also significant. Most of these associations remained statistically significant after adjusting for the multiple confounders that were included in the models (Table 2). The data suggest that asthma is associated with low birth weight both through associations with slow intrauterine growth and through preterm labor/delivery.

For the asthmatic mothers, increased odds for preterm labor, placenta previa, and hypertensive disorders of pregnancy also persisted after adjustment for confounding variables (Table 3). The odds for pre-eclampsia and pregnancy-induced hypertension still exceeded twofold after adjustment. The adjustments also had little effect on the excess risk of Cesarean section or hospital stay > 3 d (the median stay) found for the asthmatic women.

In the calendar years 1989 to 1992, some mothers presumably had more than one delivery. We were unable to perform record linkage for multiple deliveries because of confidentiality of personal identifiers. Although we have no convincing reason to suspect these multiple deliveries affected our results, we repeated the analysis, restricting the data to primiparas only. Analysis was also performed for each calender year separately. Most of the results we reported above did not change substantially in either analysis, though maternal asthma did not achieve statistical significance for some variables for all

years. For example, the adjusted odds ratios (95% confidence intervals) for maternal asthma with preterm infant were 1.62 (1.16 to 2.27) for 1989, 1.66 (1.26 to 2.19) for 1990, 1.15 (0.88 to 1.51) for 1991, and 1.32 (1.04 to 1.68) for 1992. For pre-eclampsia, they were 1.13 (0.50 to 2.56) for 1989, 2.00 (1.18 to 3.14) for 1990, 3.51 (2.13 to 5.80) for 1991 and 2.12 (1.36 to 3.29) for 1992. Among the primiparas, adjusted odds ratios (95% confidence intervals) for maternal asthma were 1.89 (1.36 to 2.64) for the outcome pre-eclampsia, 1.71 (1.11 to 2.63) for transient hypertension of pregnancy, 1.88 (1.45 to 2.43) for pregnancy-induced hypertension, and 2.09 (1.35 to 3.24) for small-for-gestational age.

DISCUSSION

In this historical cohort study, we found the pregnancies of asthmatic women to be associated with increased risk of adverse outcomes such as preterm birth, low birth weight, very-small- and small-for-gestational age, congenital anomalies, and increased hospital stay. Maternal asthma was also associated with increases in hypertensive disorders of pregnancy, placenta previa, and cesarean delivery.

Strengths of the present study include: (*1*) large sample size (largest of all studies reported on the subject); (*2*) historical cohort design; (*3*) exclusion of multiple births that are likely to complicate the interpretation of the results; (*4*) population-based analysis that reflects maternal asthma as it is managed in the general population; (*5*) consistency of associations from year to year (1989 to 1992); (*6*) extensive control for potentially confounding variables, including maternal age, maternal education, marital status, parity, race/ethnicity, diabetes mellitus, preexisting hypertension, and cigarette smoking and substance and alcohol use during pregnancy, as well as others depending on the nature of the outcome.

Set against these strengths are limitations inherent in administrative databases. Such data are prone to some degree of coding errors (17), which may be random or may contain systematic biases. The prevalence of asthma among these parturient women (0.5%) is consistent with estimates of 0.4 to 1.3% obtained by others for asthma in pregnancy (1, 2, 18), although it is somewhat on the low side. We believe that mild or intermittent asthma is more likely to have been missed and that clinically significant disease is more likely to be included in the records from the delivery hospitalization. Specific data on the course of asthma during pregnancy would be of interest, but they were not available.

Most studies of asthma in general population samples report higher prevalences than the rates reported for asthma during pregnancy. It should be noted, however, that the prevalence rate of asthma in the general population and the rate of asthma complicating pregnancy are different phenomena.

Earlier studies of the relationship between maternal asthma and adverse infant and maternal outcomes have yielded conflicting results (2, 19–25). The most obvious difference between those reporting an association and those who did not is that in the latter group, the asthma was aggressively managed. However, most of these studies did not control for important confounding variables, making interpretation somewhat uncertain.

Recently, Kramer and colleagues (25) reported a positive association between symptoms suggestive of asthma and idiopathic preterm labor. Curiously, they did not find significant associations between airway responsiveness to methacholine and idiopathic preterm labor. The reason for the disparate relationships between these two measures of asthma and idiopathic preterm labor is not clear.

The Kaiser-Permanente Prospective Study of Asthma during Pregnancy Project (2) failed to demonstrate an association between any of the infant and maternal outcomes and asthma complicating pregnancy. Asthma in that study population was well managed and aggressively controlled. However, the results of such a study with controlled asthma may not be generalizable to the broader population of pregnant asthmatics. Moreover, a close scrutiny of the numbers reported in their article reveals that asthmatic women as compared with the control women were more likely to develop pre-eclampsia, and to have a preterm, low-birth weight, or small-for-gestational-age infant (odds ratios around 1.6), though the results did not achieve statistical significance with the smaller number of subjects in the study. Unfortunately, we had no data on the extent of treatment of the asthmatic mothers, and we could not examine its effect on pregnancy outcomes.

Despite the associations of asthma with adverse infant outcomes reported here, neonatal and infant death rates were previously found to be comparable in these asthmatic and control mothers (3). Still births, another important outcome, were not included in this data set.

The pathophysiologic mechanisms that could explain the relationships between maternal asthma and adverse infant and maternal outcomes include (*1*) a common underlying etiology for the irritability or hyperactivity of both uterine and bronchial smooth muscles, (*2*) hypoxia secondary to maternal asthma, (*3*) release of bioactive mediators, and/or (*4*) medications used to treat asthma during pregnancy.

As described by Kramer and colleagues (25), irritability or hyperactivity of both uterine and bronchial smooth muscle could be common manifestations of an underlying diathesis in the mothers (atopic or otherwise) that increases intramuscular resistance in the myometrial vessels, which could also be related to a heightened myometrial tension. Such a hypothesis is further supported by the similarity of pharmacologic agents, particularly β-agonists, used to treat asthma and some of the adverse infant and maternal outcomes (e.g., preterm labor). Moreover, agents that cause constriction of airway smooth muscle (e.g., prostaglandin $F_{2\alpha}$) also cause contraction of uterine smooth muscle.

The hyperreactivity model, although intuitively attractive, seems to be inadequate in explaining all of the observed associations between adverse infant and maternal outcomes and maternal asthma. For example, if this model operates singly, one would expect an association of maternal asthma with preterm labor but not with intrauterine growth retardation (very-small- and small-for-gestational age). However, in our study population, maternal asthma was found to be associated with both preterm infant and intrauterine growth retardation (as defined by the fetal growth ratio index). This finding suggests that an additional mechanism (probably hypoxia) plays a role in the pathogenesis of low birth weight. This argument is further supported by our finding of an association between placenta previa and maternal asthma. Placenta previa has been reported to be more prevalent in pregnancies of women residing at high altitude (26).

The significant association between maternal asthma and congenital anomalies other than deformations could be due to hypoxic effects on organogenesis. However, this finding needs to be confirmed by other studies since organogenesis takes place early in life. If confirmed, the possible teratogenicity of commonly used drugs might need further investigation. It is notable that the relative risk is small, and to date no specific malformation syndrome has been identified.

The proposed pathogenesis of pre-eclampsia or hypertensive disorders of pregnancy in relation to asthma is more complex and highly speculative. Constriction of airway smooth

muscle during asthma attacks may be caused by the local release of bioactive mediators. Among the substances implicated are platelet-activating factor, histamine, acetylcholine, kinins, adenosine, tachykinins, and leukotrienes (27). Of interest is the fact that leukotrienes are also implicated in the genesis of pregnancy-induced hypertension (28, 29).

Medications used to treat asthma during pregnancy have been suggested as a responsible agent for the probable adverse infant and maternal outcomes attributable to maternal asthma (23, 30, 31). However, data from well designed and well executed studies showed, if anything, that asthmatic pregnant women who were treated with antiasthmatic drugs (β-agonists, theophylline, or steroids) had lower adverse infant and maternal outcomes than did those without treatment or those in the nonasthmatic control groups (13, 22, 32, 33).

In conclusion, the results of this study strongly suggest that maternal asthma complicating pregnancy is a significant risk factor for several adverse pregnancy outcomes. Physicians caring for mothers with asthma or their neonates should be aware of these risks. Further work is needed to confirm the specific risks and to elucidate their underlying pathogenesis.

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