

Outcomes of Pregnancy in Asthmatic Women

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Asthma probably is the most common potentially serious medical complication of pregnancy. This article reviews the literature on the maternal and perinatal effects of asthma during pregnancy. Adverse effects of asthma may be, in part, a function of asthma therapy, especially in the case of long-term oral corticosteroid administration. The effects of asthma medications during pregnancy are discussed elsewhere in this issue.

Existing studies on the effects of asthma on pregnancy outcomes have had inconsistent results in regard to perinatal mortality, prematurity, low birth weight, neonatal hypoxia, cesarean delivery, hemorrhage, preeclampsia, and other complications. Until recently, there have been few large, prospective studies of asthma during pregnancy. Many of the older studies have several methodologic inadequacies, including low power; lacking or inadequate control for confounders; little information regarding asthma severity, management, or control; and time frames that do not reflect current management.

Studies before 1990

In 1961, Schaefer and Silverman [1] published their study of 293 patients who had asthma who were managed from 1953 to 1959. This descriptive study did not use any statistics, but they found a slightly higher incidence of spontaneous abortion (11.0% versus 9.4%) and low birth weight (8.9% versus 6.2%) among

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the cohort that had asthma. In 1970, Gordon and colleagues [2] compared outcomes for 265 births among women who had asthma with 30,861 controls. They found no significant increase in prematurity, but the perinatal mortality rate among asthmatics (5.9%) was increased significantly compared with controls (3.2%).

Bahna and Bjerkedal [3] used the Medical Birth Registry of Norway to examine pregnancy outcomes for births during 1967 and 1968. Their 1972 study had 381 women who had asthma and 112,530 control subjects. The cohort with asthma had significantly more hyperemesis gravidarum (2.1% versus 0.8%), hemorrhage (4.7% versus 2.2%), preeclampsia (10.5% versus 4.7%), preterm birth (7.4% versus 5.0%), hypoxia at birth (1.6% versus 0.7%), and low birth weight (7.1% versus 3.7%) compared with controls. There were no significant differences for malformations, birth injury, or perinatal mortality rates.

In 1986, Dombrowski and colleagues [4] published a study that was designed to evaluate the effects of theophylline on the incidence of preeclampsia. They reported 153 pregnancies among women who had asthma compared with 116 controls born from 1982 to 1985. There were no differences in gestational age at birth or birth weight. The frequency of preeclampsia was decreased significantly among the cohort that was treated with theophylline.

A Finnish prospective study in 1988 by Stenius-Aarniala and Teramo [5] reported results for 198 births from 1978 to 1982 among asthmatics and 198 controls who were matched for age and parity. Asthma was classified as very mild, mild, moderately severe, and severe. The incidence of preeclampsia was significantly higher among those who had severe asthma (29%) compared with those who had very mild asthma (9%). It also was significantly more common among those who received systemic steroids (25%) than among those who did not (10%). Cesarean sections were increased significantly among women who had asthma (28% versus 17%). There were no differences in regards to gestational age at delivery, birth weight, perinatal death, low Apgar score, respiratory difficulty, and malformations.

Studies from 1990 through 1999

In 1990, Lao and Huengsborg [6] reported a retrospective study of 87 gravidas who had asthma and 87 controls who delivered in Hong Kong from 1984 to 1987. They reported an increased incidence of birth weight of less than 2500 g (10.3% versus 1.1%) and cesarean delivery (25.3% versus 9.2%) among asthmatics. There were no significant differences in gestational age at delivery, mean birth weight, postpartum hemorrhage, or perinatal complications.

Starting in 1990, the Schatz group began the first of many contributions to the literature on asthma in pregnancy [7]. This was a prospective study of 360 pregnancies from 1978 to 1984. Spirometry was performed; a small ($r=0.11$), but significant, direct correlation was demonstrated between birth weight and individual mean percent predicted forced expiratory volume in 1 second (FEV₁)

during pregnancy. No significant relationships were observed between lower FEV₁ and the incidences of preterm birth or preeclampsia. By regression analysis, smoking (odds ratio [OR], 3.2) and lower FEV₁ (OR, 3.0) were associated independently with birth weights in the lower quartile.

In 1992 Mabie and colleagues [8] published a retrospective study of 200 women who delivered between 1986 and 1989. The frequency of cesarean section was increased significantly among women who had moderate or severe asthma compared with those who had mild asthma (75% versus 33%). The frequency of intrauterine growth retardation (IUGR) was increased significantly among the cohort that moderate and severe asthma (16%) compared with women who had mild asthma (4%), but there was no differences in the rates of preterm delivery or preeclampsia.

In 1992, Perlow and colleagues [9] retrospectively identified 81 asthmatics and 130 control subjects from 1985 to 1990. Of the gravidas who had asthma, 31 were considered to be steroid dependent. Gestational diabetes (OR, 19.1; 95% confidence interval [CI], 1.9–138.1) and primary cesarean section (OR, 2.6; 95% CI, 1.1–6.6) were increased among the steroid-dependent group compared with controls. Preeclampsia and IUGR were not increased significantly. Compared with controls, the frequency of delivery at less than 37 weeks' gestation was increased among the group that was not steroid dependent (OR, 4.0; 95% CI, 1.1–15.5) and was increased markedly among the steroid-dependent group (OR, 29.9; 95% CI, 8.6–111.3). These investigators were the first group to report the effects of asthma on severe prematurity; compared with controls, there was a fourfold, nonsignificant increase of delivery at less than 32 weeks' gestation for gravidas who had asthma.

Lehrer and colleagues [10] used a computerized database of 21,115 women who delivered from 1987 to 1991. Of these, 136 had asthma during pregnancy. Pregnancy-induced hypertension was increased (OR, 2.52; 95% CI, 1.47–4.35) among the asthma cohort when logistic regression methods controlled for the confounding effects of ethnicity, age, parity, and prepregnancy weight. Doucette and Bracken [11] conducted a prospective cohort study of 3891 women who delivered a singleton birth from 1980 to 1982, of whom 31 has asthma. They found no association of asthma with birth weight, and reported a nonsignificant trend for preterm delivery.

In a prospective study, Jana and colleagues [12] reported their experience in India for 182 asthmatics and 364 controls that delivered from 1983 to 1992. There were no significant differences in regards to mode of delivery, prematurity rate, low birth weight, or perinatal mortality. There was a significant decrease in birth weight (2469 ± 571 g versus 2842 ± 494 g) among the 15 gravidas who had uncontrolled, severe asthma who required hospitalization.

In 1995, Schatz and colleagues [13] published a prospective, controlled inception cohort study of 486 asthmatics and 486 matched controls from 1978 to 1989. This study was important because it was large, prospective, and used spirometry and active management of patients who had asthma. Asthma was not associated significantly with increased preeclampsia, perinatal mortality, preterm birth, low

birth weight, IUGR, or congenital malformations. The investigators suggested that the perinatal outcomes for women who had actively managed asthma are comparable to those for the nonasthmatic population.

In 1996, Stenius-Aarniala and colleagues [14] reported outcomes for 504 pregnant women who had asthma that was managed by pulmonary specialists and 237 healthy parturients from 1982 to 1992 in Finland. There were no significant differences for length of gestation, postpartum hemorrhage, low birth weight, or nonelective cesarean section. Forty-seven women who had asthma had an acute attack during pregnancy; the frequency of exacerbations increased during pregnancy until 21 to 24 weeks' gestation, and then declined until 40 weeks' gestation. Women who used inhaled corticosteroids had a significant reduction in the risk of having an exacerbation (relative risk [RR], 0.22; 95% CI, 0.11–0.44).

In a 1998 publication, Minerbi-Codish and colleagues [15] reported their prospective study that was conducted during 1993 and 1994. Forty-nine patients had mild asthma, 36 had moderate asthma, and 16 had severe asthma; there were 77 control subjects. According to multivariate analyses, there were no significant associations of asthma to birth weight of less than 2500 g, preterm delivery, small for gestational age neonates (SGAs), or cesarean section rate. Asthmatic women were significantly more likely to suffer from respiratory and urinary tract infections (RR, 10.6).

A 1998 retrospective cohort study by Alexander and colleagues [16] was conducted in Canada between 1991 and 1993. This cohort included 3709 controls; 375 asthmatics who took no medication; 303 asthmatics who took β -agonists only; and 139 asthmatics who took "steroids," which presumably included inhaled and systemic corticosteroids. No statistical differences were found for any asthma group regarding preterm birth, gestational diabetes, low birth weight, respiratory distress syndrome, congenital anomalies, or cesarean section rate. Neonatal jaundice was increased among the group that was treated with steroids (OR, 1.9; 95% CI, 1.1–3.4). Antepartum hemorrhage was increased (OR, 2.2; 95% CI, 1.3–3.7) among the cohort that received steroids, and postpartum hemorrhage was increased (OR, 1.9; 95% CI, 1.3–2.7) among asthmatic women who took no medication, after controlling for confounders by means of logistic regression analysis.

In contrast, another study that was published in 1998 found multiple adverse maternal and perinatal associations. Demissie and colleagues [17] reported a large analysis of singleton live deliveries in New Jersey hospitals between 1989 and 1992 using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes linked with birth certificates. A total of 2289 had a code for asthma, and 9156 controls were selected randomly. After controlling for the effects of confounding variables, maternal asthma was associated significantly with preterm delivery (OR, 1.36; 95% CI, 1.18–1.55), SGAs (OR, 1.26; 95% CI, 1.10–1.45), congenital anomalies (OR, 1.37; 95% CI, 1.12–1.68), and increased neonatal length of stay (OR, 1.44; 95% CI, 1.25–1.65). Adverse maternal outcomes included preeclampsia (OR, 2.18; 95% CI, 1.68–2.83), placenta previa (OR, 1.71; 95% CI, 1.05–2.79), cesarean delivery (OR, 1.62; 95% CI, 1.46–

1.80), and increased length of stay (OR, 1.86; 95% CI, 1.6–2.15). No information was available regarding asthma severity or management.

Studies since 2000

Wen and colleagues [18] used the Canadian Institute for Health Information and *ICD-9-CM* codes to identify women who had asthma and controls from 1989 to 1996. Eight thousand six hundred and seventy-two gravidas who had asthma were compared with 34,688 controls. Logistic regression analysis was used to control for potential confounding factors. Asthma was found to be associated with multiple adverse pregnancy outcomes: preterm labor (OR, 1.78; 95% CI, 1.53–2.07), preeclampsia (OR, 1.84; 95% CI, 1.64–2.05), gestational diabetes (OR, 2.26; 95% CI, 2.02–2.53), placenta previa (OR, 1.50; 95% CI, 1.11–2.04), abruptio placenta (OR, 1.63; 95% CI, 1.35–1.96), cesarean delivery (OR, 1.48; 95% CI, 1.40–1.57), and postpartum hemorrhage (OR, 1.51; 95% CI, 1.36–1.68). There was no significant increase in fetal deaths.

Kallen and colleagues [19] used the Swedish Medical Birth Registry and the Hospital Discharge Register to collect data for births between 1984 and 1995. This study used multiple criteria for identifying subjects who had asthma. In the total asthma cohort ($n=36,985$), they found an increased incidence of preeclampsia (OR, 1.15; 95% CI, 1.08–1.23), maternal diabetes (OR, 1.34; 95% CI, 1.17–1.54), preterm birth at less than 37 weeks' gestation (OR, 1.15; 95% CI, 1.09–1.21), low birth weight of less than 2500 g (OR, 1.21; 95% CI, 1.14–1.29), and postterm birth at greater than 41 weeks' gestation (OR, 1.25; 95% CI, 1.19–1.31), but not congenital malformations (OR, 1.05; 95% CI, 0.99–1.10). The ORs were all higher for these outcomes in the 1396 asthmatic mothers who were identified in the hospital discharge registry and the antenatal records, which were believed to represent "the most certain and severe cases of asthma during pregnancy." No information was presented regarding asthma management in these patients..

Liu and colleagues [20] used *ICD-9-CM* codes and a comprehensive administrative database to identify 2193 gravidas who had asthma and 8772 controls in Quebec, Canada from 1991 to 1996. After adjusting for potential confounders, asthma was associated with increased preterm births (OR, 1.40; 95% CI, 1.18–1.66), very small for gestation age (OR, 1.9; 95% CI, 1.47–2.44), large for gestational age (OR, 1.17; 95% CI, 1.01–1.35), preeclampsia (OR, 1.77; 95% CI, 1.33–2.35), and chorioamnionitis (OR, 2.75; 95% CI, 2.31–3.27). There were no significant associations for congenital anomalies, antepartum hemorrhage, or postpartum hemorrhage.

In 2001, Olesen and colleagues [21] used the Birth Registry data from Denmark for 303 asthmatics who gave birth between 1991 and 1996. Compared with controls, there were no significant differences for gestational age or birth weight. Among the 78 women who decreased asthma medications during pregnancy, birth weight decreased significantly by 116.9 g (95% CI, 15.9–217.8).

Data on pregnancy outcomes were gathered (1997–1999) during the recruitment phase of the Childhood Asthma Prevention Study by Mihrshahi and colleagues [22]. There were 340 pregnancies of asthmatic mothers and 269 controls. Hypertension was more common among asthmatics. There were no significant differences for gestational diabetes, labor or delivery complications, or adverse perinatal outcomes.

Norjavaara and de Verdier [23] reported data from the Swedish Medical Birth Register for 1995 to 1998. This study was limited to the 2968 mothers who reported using inhaled budesonide during pregnancy; therefore, it is not applicable for answering questions about general asthma outcomes during pregnancy. Because the subjects in this study required an inhaled corticosteroid, they presumably had persistent asthma. Therefore, if more severe asthma increases the likelihood of pregnancy complications, the pregnancy outcomes in this study would be expected to be worse than studies that also enrolled subjects who had mild intermittent asthma. Nonetheless, there were no clinically significant differences in birth weight, gestational age, or stillbirths in these patients compared with all pregnancies in the Swedish Medical Birth Register for those years.

The risk of preterm delivery was examined by Sorensen and colleagues [24] in a nested case control study of women who participated in screening protocol for neural tube defects and Down's syndrome during 1994 and 1995. Four hundred and twenty-four controls were compared with 312 women who had delivered early. Significantly more subjects had asthma ($n=20$) in the cohort who gave birth early compared with controls ($n=14$) (OR, 2.37; 95% CI, 1.15–4.88) after adjusting for age, ethnicity, parity, Medicaid payment status, and smoking.

In a 2003 prospective study, Murphy and colleagues [25] reported outcomes for 138 pregnancies that were complicated by asthma compared with 44 controls. Among gravidas who were not treated with inhaled corticosteroids, female newborn birth weights (3094 ± 120 g) were reduced significantly ($P=.027$) compared with controls (3528 ± 86 g) and those who were treated with inhaled corticosteroids (3375 ± 90 g). In contrast, gravidas who were not treated with inhaled corticosteroids had larger male neonates (3701 ± 89 g) compared with controls (3602 ± 166 g) and those who were treated with inhaled corticosteroids (3446 ± 88 g; $P=.192$).

Two recent, large, multicenter, prospective cohort studies have evaluated the effects of maternal asthma on perinatal outcomes [26,27]. These studies were unique in that they contained information regarding asthma severity and management. In 2003, Bracken and colleagues [26] reported on 1333 women who had no history of asthma, and 873 pregnant women who had asthma. Approximately half of the study population was classified as having intermittent asthma (no asthma symptoms or treatment during pregnancy). Preterm delivery was not associated with asthma diagnosis or severity; however, oral corticosteroid use was associated with a reduction in gestation of 2.22 weeks ($P=.001$), and theophylline use was associated with a reduction of 1.11 weeks ($P=.002$). The diagnosis of asthma was not associated with a significant increase in SGAs. Increasing asthma severity and symptoms were associated with SGAs; those who

had daily symptoms (OR, 2.25; 95% CI, 1.25–4.06) and those who had moderate, persistent asthma (OR, 2.01; 95% CI, 1.11–3.65) manifested increased risks. No specific medication type was observed to lead to an increased risk of fetal growth restriction. In a related publication, Triche and colleagues [28] reported that asthma was not associated with an increased incidence of preeclampsia; however, preeclampsia was increased significantly among the cohort who had daily asthma symptoms (OR, 3.36; 95% CI, 1.24–9.14) and among those who received theophylline (OR, 1.16; 95% CI, 1.02–1.33). These data suggest that poor asthma control—by causing acute or chronic maternal hypoxia—may be the most remedial responsible factor, and support the important generalization that adequate asthma control during pregnancy is important in improving maternal–fetal outcome.

The National Institute of Child Health and Human Development [NICHD] and National Heart, Lung, and Blood Institute [NHLBI] conducted a multicenter, prospective, observational cohort study that involved 16 centers between 1994 and 1999. They enrolled 873 subjects who had mild asthma, 814 subjects who had moderate asthma, 52 subjects who had severe asthma, and 881 nonasthmatic controls. Because (1) prematurity is a leading cause of perinatal mortality and long-term neurologic morbidity in children with very preterm births (<32 weeks' gestation) account for most of the morbidity and mortality, and (2) asthma during pregnancy has been associated with a fourfold increase of deliveries of less than 32 weeks' gestation [9], preterm delivery of less than 32 weeks' gestation was the primary outcome of this study. Reporting on the perinatal outcomes in this study in 2004, Dombrowski and colleagues [27] found no significant differences in the rates of preterm delivery at less than 32 weeks' gestation or at less than 37 weeks' gestation. Of all of outcomes that were explored (including preterm delivery, gestational diabetes, preeclampsia, preterm labor, chorioamnionitis, oligohydramnios, cesarean delivery, low birth weight, small for gestational age, and congenital malformations), only cesarean delivery rate was increased in the group that had moderate to severe asthma (OR, 1.4; 95% CI, 1.1–1.8). There were no significant differences for neonatal outcomes, except for discharge diagnosis of neonatal sepsis among the group that had mild asthma—a finding that may be related to type I error. Among the cohort that had severe asthma, there was a significantly increased incidence of gestational diabetes (OR, 3.0; 95% CI, 1.2–7.8) and delivery at less than 37 weeks' gestation (OR, 2.2; 95% CI, 1.2–4.2), after adjusting for confounding variables by means of logistic regression analyses.

In a secondary analysis of this study, Schatz and colleagues [29] reported that oral corticosteroid use was associated significantly with preterm delivery at less than 37 weeks' gestation (OR, 1.54; 95% CI, 1.02–2.33) and birth weight of less than 2500 g (OR, 1.80; 95% CI, 1.13–2.88). In same cohort of patients, those who had mild asthma had an exacerbation rate of 12.6% with a hospitalization rate of 2.3% [30]. Those who had moderate asthma had an exacerbation rate of 25.7% and a hospitalization rate of 6.8%. Severe asthmatics ($n=52$) had exacerbation and hospitalization rates of 51.9% and 26.9%, respectively. During the course of pregnancy, 23.0% of women had an improvement in asthma severity,

and 30.3% had an increase in asthma severity. One of the most important conclusions to be drawn from this study is that pregnant asthmatic patients, even those who have mild or well-controlled disease, need to be monitored closely during pregnancy.

The NICHD/NHLBI study had excellent maternal and perinatal outcomes, despite a high frequency of asthma exacerbations. These findings do not contradict the possibility that suboptimal control of asthma during pregnancy is associated with an increased risk to the mother or baby. This study did find a relationship between lower FEV₁ during pregnancy and an increased risk of gestational hypertension and prematurity [31]. The studies by Bracken and colleagues [26] and Dombrowski and colleagues [27] suggest that if possible, asthma should be controlled without oral corticosteroids. Both studies indicate that classification of asthma severity with therapy that is tailored according to asthma severity can result in excellent perinatal and maternal outcomes. This generally confirms the findings of two earlier and smaller prospective cohort studies, in which the asthma was managed by asthma specialists [13,14].

Putting the literature into perspective

There is considerable consistency among prospective studies of the effects of asthma on maternal and perinatal outcomes. Eight prospective studies that reported maternal and neonatal outcomes with at least 100 subjects, in locations at or near sea level, have been published in the English literature (Table 1). One can conclude from these studies that populations that have mild or moderate asthma during pregnancy can have excellent maternal and perinatal outcomes. The two largest studies, by Dombrowski and colleagues [27] and Bracken and colleagues [26], reported an increase in preterm delivery at less than 37 weeks' gestation among subjects who had severe asthma or who required oral corticosteroids. In addition, two studies reported an increase in preeclampsia [5,26], although one of these only found this in patients who had daily symptoms [26]. Three studies reported increased cesarean delivery [5,14,27], although one of these was only in patients who had moderate to severe asthma [27]. One study reported an increased incidence of gestational diabetes with severe asthma [27], and one found an increased risk of SGAs in mothers who had daily asthma symptoms [26].

In contrast, there is much less consensus among retrospective studies of asthma in pregnancy. Nearly every possible pregnancy complication has been associated with asthma in at least one retrospective publication. Studies that enrolled patients after the 1993 National Asthma Education and Prevention Program [NAEPP] recommendations [32] for anti-inflammatory management tended to have fewer adverse pregnancy outcomes associated with asthma. This again supports the concept that optimal asthma management can mitigate adverse pregnancy outcomes. Patients who have poorly controlled asthma that is complicated by severe exacerbations are at significant risk for maternal and fetal morbidity and mortality.

Table 1
Prospective cohort studies reporting obstetric and neonatal outcomes for pregnancies complicated by asthma

	Dombrowski et al, 2004 [27] (n = 1739)	Bracken et al, 2003 [26] (n = 872)	Stenius-Aarniala et al, 1996 [14] (n = 504)	Schatz et al, 1995 [13] (n = 486)	Mihreshahi et al, 1993 [22] (n = 340)	Jana et al, 1995 [12] (n = 182)	Stenius-Aarniala & Teramo, 1988 [5] (n = 181)	Minerbi-Codish et al, 1998 [15] (n = 101)
Preterm <32 weeks*	No							
Preterm <37 weeks*	No (yes if severe)	No (yes if oral steroids)	No	No	No	No	No	No
Preeclampsia	No	No (yes if daily symptoms)	No	No	No	Yes	Yes	No
Cesarean delivery	Yes (if moderate or severe)		Yes, if elective		No	No	Yes	No
Gestational diabetes	No (yes if severe)		No	No		No	No	No
Small for gestational age	No	No (yes if daily symptoms)		No		No	No	No
Malformation	No		No	No		No		No
Antenatal hemorrhage	No		No			No	No	
Postnatal hemorrhage	No			No			No	
RDS/HMD	No			No			No	
NEC	No			No				
Perinatal death	No		No	No		No	No	
NICU admission	No		No		No		No	

Abbreviations: NEC, necrotizing enterocolitis; NICU, neonatal ICU; RDS/HMD, respiratory distress syndrome, hyaline membrane disease.

A potential explanation for the inconsistencies among previous studies with regard to the effect of asthma on obstetric and neonatal outcomes is that many studies of asthma during pregnancy did not classify asthma severity. Classification of asthma severity has important clinical implications with regard to asthma morbidity and in tailoring optimal treatment regimens [32–34]. Failure to classify severity may result in suboptimal asthma control, and thereby, increases the risks for adverse maternal or neonatal outcomes. Oral corticosteroid treatment may confound maternal and neonatal outcomes. Some positive findings may be due to chance or confounders, such as ethnicity, smoking status, socioeconomic status, and hypertension. Prospective studies may have had fewer significant adverse associations because of better asthma surveillance and treatment.

There are important caveats when interpreting this literature. The excellent maternal and perinatal outcomes of recent studies were achieved at centers that tended to manage asthma actively in pregnancy. As described elsewhere in this issue, NAEPP recommendations for active asthma management include step therapy, anti-inflammatory treatment for gravidas who have persistent asthma, assessment of pulmonary function by way of peak flow meters or spirometry, patient education, and avoidance of asthma triggers. In addition, women who enroll in research studies tend to be more compliant and better motivated than the general public; compliance with prescriptions has been associated with better outcomes among women who have asthma [21]. The lack of more adverse outcomes among gravidas who have severe asthma also may be a function of the small numbers of this subgroup, and the resulting lack of power to find adverse outcomes that were statistically significant. Nonetheless, these prospective studies are reassuring in their consensus of good pregnancy outcomes among women who have asthma. These studies do not suggest that asthma should be considered to be a benign condition, because active asthma management was a part of these studies.

Summary

Mild and moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes, especially if patients are managed according to contemporary NAEPP recommendations. Severe and poorly controlled asthma may be associated with increased mild prematurity (<37 weeks' gestation), a need for cesarean delivery, preeclampsia, and growth restriction. Poorly controlled asthma and severe asthma exacerbations can result in maternal morbidity and mortality, which can have commensurate adverse pregnancy outcomes.

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