

A Comprehensive Analysis of Adverse Obstetric and Pediatric Complications in Women with Asthma

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Rationale: Previous studies have raised concern that women with asthma have increased risks of adverse obstetric and pediatric complications, but these have generally been underpowered.

Objectives: To quantify risks of major adverse pregnancy outcomes and obstetric complications in women with and without asthma.

Methods: We extracted information on 281,019 pregnancies from the Health Improvement Network database between 1988 and 2004. We analyzed the data using logistic regression.

Measurements and Main Results: In 37,585 pregnancies of women with asthma compared with 243,434 pregnancies of women without asthma, risks of stillbirth and therapeutic abortion were similar; however, the risk of miscarriage was slightly higher (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.06–1.13). Risks of most obstetric complications (placental abruption, placental insufficiency, placenta previa, preeclampsia, hypertension, gestational diabetes, thyroid disorders in pregnancy, and assisted delivery) were not higher in pregnancies of women with asthma compared with those without asthma, with the exception of increases in antepartum (OR, 1.20; 95% CI, 1.08–1.34) or postpartum (OR, 1.38; 95% CI, 1.21–1.57) hemorrhage, anemia (OR, 1.06; 95% CI, 1.01–1.12), depression (OR, 1.52; 95% CI, 1.36–1.69), and caesarean section (OR, 1.11; 95% CI, 1.07–1.16). Risks of miscarriage, depression, and caesarean section increased moderately in women with more severe asthma and previous asthma exacerbations.

Conclusions: We found some increased risks in women with asthma that need to be considered in the future; however, our results indicate that women with asthma have similar reproductive risks compared with women without asthma in the general population for most of the range of outcomes studied.

Keywords: asthma; asthma severity; obstetric/pregnancy complication; adverse pregnancy outcomes; case-control

Since Bahna and Bjerkedal's 1972 report (1) showing increased risks of obstetric complications in women with asthma, the management of asthma through new treatment medications and optimization of drug doses has improved considerably. More recent studies of pregnancy have shown mixed results (2–19), but have still indicated that risks of preeclampsia (4, 7, 9, 10, 14, 16, 17), hemorrhage (10, 13), gestational diabetes (4, 7, 10, 14), perinatal mortality (4, 11), and other obstetric complications (3, 6, 7, 9, 10, 13) may be increased in women with asthma, which is alarming because the prevalence estimates of current asthma in women of child-bearing age have increased from 3 to 8% over the past 30 years (20). Thus far, very few studies investigating obstetric complications in women with asthma have adjusted for potential

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Asthma now affects up to 10% of pregnant women, and although previous studies have raised concern that women with asthma have an increased risk of adverse obstetric and pediatric complications, they have generally been underpowered.

What This Study Adds to the Field

We found reassuring evidence of no increased risks for most adverse pregnancy outcomes and obstetric complications in women with asthma, including stillbirth and therapeutic abortion; however, women with asthma have a modest increased risk of miscarriage.

confounding factors (5, 19, 21) or have had the ability to assess whether risks differ by the degree of both asthma severity and the occurrence of exacerbations (2, 16, 17, 19, 21), and none have had adequate study population size to estimate individual risks of miscarriage, stillbirth, and therapeutic abortion.

Using data on over 280,000 pregnancies from women in the general U.K. population, we present the results of a comprehensive analysis of the reproductive experience of women with asthma to determine the precise magnitude of their risks of obstetric complications and adverse pregnancy outcomes compared with women without asthma. We have also assessed the effects of asthma severity and acute asthma exacerbations on pregnancy risks.

Some of the results of this study have been previously reported in the form of an abstract (22).

METHODS

Dataset

The Health Improvement Network (23) (THIN) is a computerized primary care database of anonymous patient records, with a high standard of validated recording of medical diagnoses, medical events, and prescriptions (24). In data collection for this study, 255 general practices across England and Wales contributed longitudinal records for 3.9 million patients.

Study Population

We identified all women aged between 15 and 50 years contributing data from January 1, 1988, to November 30, 2004. We extracted all codes relating to stillbirth, miscarriage, and therapeutic abortion. Live births were obtained by linking birth-related codes in the women's records to births of registered children in the same household at the time of the delivery. For pregnancies ending in live births, we examined the following obstetric complications: antepartum and postpartum

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hemorrhage, placental insufficiency, placental abruption, placenta previa, preeclampsia/eclampsia, hypertension, diabetes, anemia, thyroid disorders, depression in pregnancy, caesarean section delivery, and assisted delivery.

Women were defined as having asthma if they had a medical code for asthma at any time in their general practice record. Using prospectively collected data, we extracted all prescriptions for asthma medications and codes for exacerbations during the year before each pregnancy. We categorized women into different levels of asthma severity in accordance with the British Thoracic Society asthma guidelines for medication use (25). Our three categories of asthma severity in the year before pregnancy were as follows: (1) unmedicated asthma (no prescriptions), (2) asthma medicated with at least one prescription of a short-acting β -agonist (SABA), and (3) asthma medicated with at least one prescription for an inhaled corticosteroid (ICS) with or without a long-acting β -agonist (LABA). We defined an asthma exacerbation as a code for an exacerbation or an oral corticosteroid prescription. We then categorized women as having no exacerbations in the past year or having at least one asthma exacerbation in the past year.

For each pregnancy, we extracted data on the woman's age at the pregnancy outcome, most recent smoking status, and body mass index (BMI; kg/m²) before the pregnancy, as well as socioeconomic status (quintile of Townsend deprivation index [26]). The Townsend deprivation index is a postal code-linked measure of area-level deprivation (based on car ownership, unemployment, overcrowding of residence, and property ownership), which has been extensively validated (26, 27).

Statistical Analysis

The unit of analysis was a pregnancy. If a woman had more than one pregnancy in her general practice record during the study period from January 1, 1988, to November 30, 2004, all of her pregnancies were included in the analysis. We calculated the prevalence of each pregnancy outcome as a proportion of all pregnancies. We calculated the prevalence of each obstetric complication as a proportion of all pregnancies ending in live births.

Using logistic regression in Stata 9.0 (Stata Corp., College Station, TX), we estimated odds ratios of the outcomes comparing pregnancies in women with asthma with those without. We then estimated separate odds ratios for the pregnancies of women at each level of asthma severity and for women with and without previous asthma exacerbations, compared with the pregnancies of women without asthma.

In multivariate analyses, we adjusted all models for maternal age, smoking status, and BMI before the pregnancy. We then explored effects of Townsend index (in quintiles), year of birth, multiple pregnancy (twin, triplet, quadruplet), gestation of the pregnancy, and sex of the child where appropriate, retaining only those variables that changed the odds ratios more than 10%. Because some women had more than one pregnancy during the study period, either as consecutive pregnancies or as multiple pregnancies (twins, triplets, quadruplets), we allowed for potential clustering by woman using robust standard errors (28). Missing values for covariates were fitted as a separate category and all models were refitted using women with complete data.

RESULTS

Study Population

During our study period, 187,502 women had a total of 281,019 pregnancies, with 121,092 women (64%) having one pregnancy, 46,447 women (25%) having two pregnancies, and 19,963 women (11%) having three or more pregnancies. Of all pregnancies, 207,643 (74%) ended in one or more live births, 35,272 (13%) ended in miscarriage, 37,118 (13%) ended in therapeutic abortion, and 986 (< 1%) ended in a stillbirth (Figure 1). Approximately 13% (37,585) of all pregnancies were to women with asthma. Maternal age was slightly lower in pregnancies of women with asthma compared with those of women without asthma (Table 1). Only 75% of pregnancies had information on the woman's smoking status before pregnancy, 55% had information on BMI before pregnancy, and 55% had the Townsend index quintile. For pregnancies with these covariate data, current smoking, a BMI over 25 kg/m² before pregnancy, and increased deprivation as measured by the Townsend index, were all associated with maternal asthma, although the differences were generally small. The pregnancies of mothers with asthma, however, were more likely to have data available on smoking status, BMI, and Townsend index quintile. Most pregnancies ending in live births were singleton pregnancies and there were no differences between the proportions of twin, triplet, or quadruplet pregnancies in mothers with and without asthma. Half of the live-born children were female and there was no difference in the sex profile of children with mothers with asthma and those without.

Adverse Pregnancy Outcomes and Obstetric Complications

The crude proportions of pregnancies ending in any fetal death were similar in pregnancies of women with and without asthma (27 and 26%, respectively). However, after adjusting for maternal age, smoking status, and BMI, we found a small increase in odds of miscarriage, and a marginal decrease in odds of therapeutic abortion in the pregnancies of women with asthma compared with those without asthma (Table 2).

For pregnancies ending in live births, our adjusted odds ratio estimates showed little difference in the risks of placental abruption, placenta previa, preeclampsia or eclampsia, hypertension, diabetes, thyroid disorders, and assisted delivery in the pregnancies of women with and without asthma. The pregnancies of women with asthma had a 20% increased odds of antepartum hemorrhage, a 38% increased odds of postpartum hemorrhage, a 6% increased odds of anemia, a 52% increased odds of depression, and an 11% increased odds of being delivered by caesarean section, compared with the pregnancies of women without asthma (Table 3). Placental insufficiency was recorded in only

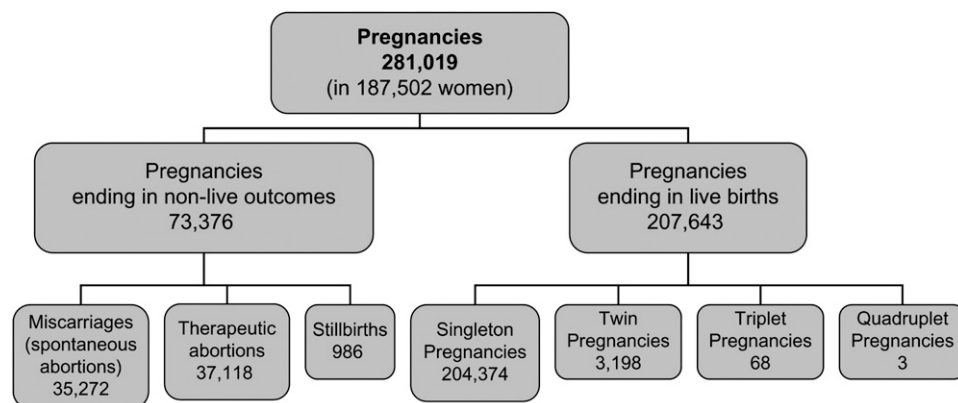


Figure 1. Pregnancies and pregnancy outcomes in the study population.

TABLE 1. CHARACTERISTICS OF PREGNANT WOMEN AND THEIR OFFSPRING

Covariate	Pregnancies in Women with Asthma (n = 37,585)		Pregnancies in women without Asthma (n = 243,434)	
	n	%*	n	%*
Maternal age at pregnancy outcome, yr				
Median (interquartile range)	28.2 (23.4–32.5)		29.3 (24.9–33.3)	
Smoking status				
Nonsmoker	17,374	58.1	112,553	62.4
Ex-smoker	2,266	7.6	11,862	6.6
Current smoker	10,238	34.3	55,876	31.0
Missing	7,707		63,143	
Body mass index, kg/m ²				
Underweight (< 18.5)	1,028	4.5	6,259	4.8
Normal (18.5–24.9)	13,235	58.3	84,081	64.0
Overweight (25–29.9)	5,291	23.3	27,862	21.2
Obese (≥ 30)	3,155	13.9	13,257	10.1
Missing	14,876		111,975	
Townsend index quintile†				
1 (least deprivation)	5,332	24.7	36,642	27.3
2	4,053	18.8	27,411	20.5
3	4,395	20.3	27,339	20.4
4	4,270	19.8	23,957	17.9
5 (most deprivation)	3,548	16.4	18,674	13.9
Missing	15,987		109,411	
Sex of child‡				
Female	13,599	49.1	89,194	48.7
Male	14,123	50.9	93,881	51.3
Singleton and multiple pregnancies§				
Singleton	26,922	98.6	177,636	98.5
Twin	388	1.4	2,631	1.5
Triplet	8	< 0.1	55	< 0.1
Quadruplet	0	< 0.1	3	< 0.1

* Proportions are of pregnancies with data for covariates

† Townsend index quintile only available for 69% of The Health Improvement Network general practices.

‡ Proportions based on live births (n = 210,797).

§ Proportions based only on pregnancies ending in live births (n = 207,643).

four pregnancies of women without asthma, and none occurred in pregnancies to women with asthma. All results presented were adjusted for maternal age, smoking status, and BMI, because other potential confounders (socioeconomic status, year of birth,

TABLE 2. PREGNANCY OUTCOMES IN WOMEN WITH AND WITHOUT ASTHMA

Pregnancy Outcome	Pregnancies in Women with Asthma (n = 37,585)		Pregnancies in Women without Asthma (n = 243,434)		Adjusted Odds Ratio* (95% CI)
	n	%	n	%	
Live birth	27,318	72.7	180,325	74.1	0.98 (0.95–1.00)
Stillbirth	138	0.4	848	0.3	1.04 (0.86–1.24)
Miscarriage†	4,967	13.2	30,305	12.4	1.10‡ (1.06–1.13)
Therapeutic abortion	5,162	13.7	31,956	13.1	0.95‡ (0.92–0.99)

Definition of abbreviation: CI = confidence interval.

* Comparing pregnancies in women with asthma to pregnancies in women without asthma; adjusted for maternal age, smoking habit, and body mass index.

† Or other early pregnancy loss (ectopic pregnancy, blighted ovum, molar pregnancy).

‡ p < 0.05.

multiple pregnancy, gestation of pregnancy, and sex of the child) had no substantial effect on the odds ratios.

Effects of Asthma Severity and Exacerbations on Pregnancy Outcomes and Complications

For the pregnancies of women with diagnosed asthma (37,585), our categorization of disease severity during the year before the pregnancy showed that most pregnancies (64%) were to women with unmedicated asthma, 13% were to women on SABA therapy only, and 24% were to women on ICS with or without LABA therapy. In the same pregnancies, 7% of pregnancies were to women with at least one recorded exacerbation in the year before the pregnancy.

When we compared pregnancy outcomes across categories of asthma severity and by asthma exacerbations (Table 4), we found that the overall increased odds of miscarriage associated with maternal asthma was restricted to medicated asthma only and that the odds were higher for women with previous exacerbations. The overall marginal decreased odds of therapeutic abortion was limited to unmedicated asthma and women with no previous exacerbations, and there was a slight increased odds of pregnancies ending in therapeutic abortion if the mother had been on SABA therapy or if she had exacerbations before the pregnancy. As a result of the increased odds of miscarriage and abortion, there was a small decreased odds of pregnancies ending in live births for women with medicated asthma or previous exacerbations.

For live births (207,643), the distributions across categories of maternal asthma severity and exacerbations were the same as those for all pregnancies (281,019). The increased odds of antepartum hemorrhage found in the overall analysis was slightly higher in women taking ICS with or without LABA therapy. The increased odds of postpartum hemorrhage found in the overall analysis was restricted to pregnancies of mothers who had less severe asthma and no exacerbations (Table 5). The overall increased odds of anemia in pregnancy was only statistically significant at the 5% level in pregnancies to women with no exacerbations before pregnancy. The odds of depression in pregnancy for women with asthma increased with higher severity and previous exacerbations, compared with pregnancies in women without asthma. Although there was no overall increased odds of placenta previa in pregnancies for women with asthma compared with those without asthma, pregnancies in women on SABA therapy and those in women with previous exacerbation conferred an increased odds compared with pregnancies in women without asthma. We also found an increased odds of thyroid disorders in pregnancies in women receiving ICS with or without LABA therapy. The increased caesarean section odds for deliveries in mothers with asthma was predominantly in deliveries to women with more severe asthma and with previous exacerbations (Table 5). When we restricted each analysis to pregnancies in women with full data for covariates, we obtained almost identical effect sizes to the overall analyses (data not shown).

DISCUSSION

Our findings in this U.K. population-based study indicate that women with asthma in general have similar risks of reproductive outcomes compared with women without asthma for most of the outcomes studied. Of concern, there was a small increased risk of miscarriage, which was higher in women with more severe asthma and previous exacerbations. However, we found no evidence for an increased risk of stillbirth in women with asthma, regardless of asthma severity or exacerbations. Other important findings include increased risks of hemorrhage, which were not

TABLE 3. OBSTETRIC COMPLICATIONS IN WOMEN WITH AND WITHOUT ASTHMA

Obstetric Complication	Pregnancies in Women with Asthma (n = 27,318)		Pregnancies in Women without Asthma (n = 180,325)		Adjusted Odds Ratio* (95% CI)
	n	%	n	%	
Antepartum hemorrhage	407	1.5	2,177	1.2	1.20 [†] (1.08–1.34)
Postpartum hemorrhage	287	1.1	1,367	0.8	1.38 [†] (1.21–1.57)
Placental abruption	27	0.1	163	0.1	1.08 (0.72–1.62)
Placenta previa	33	0.1	207	0.1	1.08 (0.74–1.57)
Preeclampsia or eclampsia	140	0.5	804	0.4	1.12 (0.93–1.34)
Hypertension during pregnancy	269	1.0	1,707	0.9	1.01 (0.88–1.15)
Diabetes during pregnancy	174	0.6	1,084	0.6	1.01 (0.85–1.21)
Anemia during pregnancy	1,890	6.9	11,486	6.4	1.06 [†] (1.01–1.12)
Thyroid disorder during pregnancy	105	0.4	558	0.3	1.23 (0.99–1.53)
Depression during pregnancy	468	1.7	1,854	1.0	1.52 [†] (1.36–1.69)
Caesarean section delivery	4,169	15.3	25,048	13.9	1.11 [†] (1.07–1.16)
Assisted delivery	1,843	6.7	11,788	6.5	1.05 (1.00–1.11)

Definition of abbreviation: CI = confidence interval.

* Comparing pregnancies in women with asthma with pregnancies in women without asthma; adjusted for maternal age, smoking habit, and body mass index.

[†] p < 0.05.

associated with asthma severity, as well as depression and caesarean section delivery in all women with asthma, which increased marginally in women with higher severity and previous exacerbations. Other increased risks for specific exposures included placenta previa and thyroid disorder; however, in consideration of the large number of outcomes studied, we cannot exclude the possibility that some findings may be due to chance.

Strengths and Limitations

Using data from general practices in the United Kingdom, we have conducted the largest general population-based study characterizing the reproductive experience of women with asthma, and we have been able to investigate the associations with differing asthma severity and acute exacerbations in these women before pregnancy. Asthma exacerbations in general may also reflect asthma severity or may result from poor adherence to medication, suboptimal prescribed treatment, lack of relief from asthma medications, or exposure to external triggers. Because asthma severity and exacerbations can change during pregnancy, we also investigated associations of obstetric complications with these measures during pregnancy, and found similar results to our overall analyses (data not shown). We were not able to investigate asthma severity and exacerbations during pregnancy for miscarriage, therapeutic abortion, or stillbirth because of the much shorter duration of gestation for these outcomes compared with gestation for live births.

In this analysis, we have quantified the individual risks of all major adverse pregnancy outcomes (stillbirth, miscarriage, and therapeutic abortion) in one study population, comparing women with asthma with women in the general population. Although THIN is a relatively new general practice database, validation studies in the General Practice Research Database (GPRD), from which over half of THIN general practices originate, have indicated that recording of births (live and stillbirths) and major diagnoses, including respiratory conditions, is accurate and complete (29–31). A recent study demonstrated that data from non-GPRD practices in THIN, including records of hypertension, diabetes, obesity, and smoking, have the same high standard of validity as data collected for GPRD practices (24). There has not been extensive validation of obstetric complications in THIN or the GPRD; however, these should also be well recorded in the database because they are major medical events that would be recorded in hospital correspondence. Although current figures of population asthma prevalence in women of childbearing age are not available in the United Kingdom, our population-based prevalences of all diagnosed asthma (13%) and currently treated asthma (5%) were similar to U.S. national figures (20). With regard to therapeutic abortion, our figures are lower than those reported in U.S. (32) and U.K. (33) national data. It is possible that ascertainment of therapeutic abortions is incomplete in this study, although recording should be fairly complete in this general practice setting because therapeutic

TABLE 4. ASSOCIATION OF ASTHMA SEVERITY AND EXACERBATIONS IN THE YEAR BEFORE PREGNANCY WITH PREGNANCY OUTCOMES

Pregnancy Outcome	Adjusted Odds Ratios* (95% CI) for Pregnancy Outcomes				
	Unmedicated Asthma (n = 23,898)	SABA-medicated Asthma (n = 4,838)	ICS/LABA-medicated Asthma (n = 8,849)	No Exacerbations (n = 34,990)	≥ 1 Exacerbation (n = 2,595)
Live birth	1.03 (1.00–1.06)	0.87 [†] (0.81–0.93)	0.90 [†] (0.86–0.95)	0.99 (0.97–1.02)	0.78 [†] (0.72–0.85)
Stillbirth	0.98 (0.78–1.23)	1.17 (0.75–1.82)	1.10 (0.79–1.55)	1.02 (0.84–1.23)	1.28 (0.72–2.28)
Miscarriage	1.03 (0.99–1.08)	1.14 [†] (1.05–1.24)	1.24 [†] (1.17–1.32)	1.08 [†] (1.05–1.12)	1.28 [†] (1.15–1.43)
Therapeutic abortion	0.93 [†] (0.89–0.96)	1.10 [†] (1.02–1.20)	0.95 (0.89–1.01)	0.94 [†] (0.91–0.97)	1.16 [†] (1.04–1.30)

Definition of abbreviations: CI = confidence interval; ICS/LABA = inhaled corticosteroid with or without long-acting β -agonist therapy; SABA = short-acting β -agonist therapy.

* Reference group is pregnancies in women with no asthma (n = 243,434). Odds ratios adjusted for maternal age, smoking habit, and body mass index.

[†] p < 0.05.

TABLE 5. ASSOCIATION OF ASTHMA SEVERITY AND EXACERBATIONS IN THE YEAR BEFORE PREGNANCY WITH OBSTETRIC COMPLICATIONS

Obstetric Complication	Adjusted Odds Ratios* (95% CI) for Obstetric Complications				
	Pregnancies by Asthma Severity			Pregnancies by Exacerbation	
	Unmedicated Asthma (<i>n</i> = 17,604)	SABA-medicated Asthma (<i>n</i> = 3,409)	ICS/LABA-medicated Asthma (<i>n</i> = 6,305)	No Exacerbations (<i>n</i> = 25,541)	≥ 1 Exacerbation (<i>n</i> = 1,777)
Antepartum hemorrhage	1.17 [†] (1.02–1.33)	1.22 (0.93–1.60)	1.27 [†] (1.04–1.55)	1.19 [†] (1.06–1.33)	1.33 (0.93–1.91)
Postpartum hemorrhage	1.47 [†] (1.27–1.71)	1.56 [†] (1.13–2.16)	1.01 (0.75–1.35)	1.42 [†] (1.24–1.62)	0.83 (0.46–1.52)
Placental abruption	1.00 (0.60–1.67)	1.26 (0.47–3.41)	1.21 (0.56–2.60)	0.99 (0.64–1.52)	2.44 (0.89–6.66)
Placenta previa	0.85 (0.49–1.45)	2.02 (1.00–4.10)	1.18 (0.61–2.28)	0.92 (0.60–1.39)	3.24 [†] (1.53–6.88)
Preeclampsia or eclampsia	1.19 (0.96–1.48)	0.96 (0.58–1.60)	1.00 (0.69–1.45)	1.15 (0.96–1.39)	0.58 (0.24–1.41)
Hypertension during pregnancy	1.04 (0.88–1.22)	0.96 (0.68–1.37)	0.95 (0.73–1.23)	1.00 (0.88–1.15)	1.04 (0.66–1.62)
Diabetes during pregnancy	1.08 (0.87–1.33)	0.63 (0.36–1.11)	1.05 (0.79–1.41)	1.00 (0.84–1.18)	1.22 (0.74–2.01)
Anemia during pregnancy	1.07 (1.00–1.14)	1.04 (0.91–1.19)	1.08 (0.97–1.19)	1.07 [†] (1.01–1.12)	1.04 (0.86–1.25)
Thyroid disorder during pregnancy	0.92 (0.69–1.24)	1.19 (0.68–2.07)	2.03 [†] (1.46–2.81)	1.19 (0.95–1.48)	1.79 (0.98–3.27)
Depression during pregnancy	1.47 [†] (1.29–1.68)	1.49 [†] (1.15–1.94)	1.64 [†] (1.36–1.97)	1.47 [†] (1.32–1.64)	2.06 [†] (1.53–2.78)
Caesarean section delivery	1.09 [†] (1.03–1.14)	1.03 (0.93–1.14)	1.24 [†] (1.15–1.33)	1.10 [†] (1.06–1.14)	1.37 [†] (1.22–1.55)
Assisted delivery	1.03 (0.97–1.10)	1.14 (1.00–1.31)	1.06 (0.96–1.18)	1.05 (0.99–1.10)	1.13 (0.94–1.36)

Definition of abbreviations: CI = confidence interval; ICS/LABA = inhaled corticosteroid with or without long-acting β -agonist therapy; SABA = short-acting β -agonist therapy.

* Reference group is pregnancies in women with no asthma (*n* = 180,325). Odds ratios adjusted for maternal age, smoking habit, and body mass index.

[†] *p* < 0.05.

abortion is a medical procedure. Miscarriage ascertainment in primary care will also be lower than the true population prevalence because early miscarriages may not be clinically reported; however, our proportion is comparable to national data (32). Although we do not anticipate any reason for differential recording of live and still births in women with and without asthma, we acknowledge the possibility that women with asthma are more likely to have miscarriages or therapeutic abortions recorded, because individuals with a chronic condition visit the general practitioner more often than those without asthma. Therefore, our odds ratio estimates for miscarriage and therapeutic abortion may be slight overestimates, but not underestimates, of the true risk.

We were not able to include estimates of premature birth and low birth weight because we were limited by a large amount of missing data for these measures. We also recognize that we had high levels of missing data for smoking, BMI, and socioeconomic status, of approximately 25 to 45%, and there were differences of approximately 5% in the amount of missing data between pregnancies in women with and without asthma, which is common in studies using general practice data. The Townsend deprivation index was only available for 176 of the 255 THIN general practices, because the process of integrating this variable into the database for research purposes was in development. However, this amount of missing data must be seen in the context of a 100% participation rate achieved through using totally anonymous data, so that we had complete data on 55 to 75% of women. This level of response and follow-up rate in a primary epidemiologic questionnaire study of pregnancy would be seen as high. In our analyses, we ensured that missing data for covariates were included as a separate category in all analyses. Because of our generous study power, we were also able to restrict analyses to women with full data. Although this restricted sample may not have been representative of the general population, we found similar effect sizes to the overall analyses.

Interpretation in Context of Other Studies

Proposed mechanisms for increased obstetric risks in women with asthma are as follows: maternal hypoxia during asthma exacerbations; abnormal smooth muscle activity of the uterus, related to similar mechanisms of airway smooth muscle in asthma; and the use of asthma medications, all of which may

have direct adverse effects on the woman during pregnancy or on the immediate viability of the fetus *in utero*. Studies estimating obstetric risks in asthma, however, have been inconsistent (1, 2, 4–19). With the exception of one analysis (4), most studies have found that risks of stillbirth (1) or perinatal mortality (1, 6, 10, 11, 17–19) were not increased in women with asthma compared with women without asthma; however, most of these studies were either not adequately powered for such assessments, with fewer than 20 perinatal deaths in women with asthma (1, 6, 11, 17), or were not controlled for potential confounders (1, 17–19). In the two largest studies of perinatal mortality, Wen and colleagues (10) found no increased risk for women with asthma after controlling for maternal age in an analysis of 233 fetal deaths, whereas Kallen and associates (4) found a small increased risk for women with asthma, after controlling extensively for confounding variables, in an analysis of 312 infant deaths, which included 103 stillbirths. No studies have conducted specific analyses of miscarriage or therapeutic abortion risks in the general female population.

Studies of obstetric complications in women with asthma compared with women without asthma have reported increased risks of placenta previa (9, 10), placental abruption (3, 7, 10), gestational diabetes (4, 7, 10, 14, 17), and hypertension (6, 7, 9, 10, 15, 19), and up to twofold increased risks of preeclampsia (4, 7, 9, 10, 14, 16, 17), which are in contrast to our findings. However, most studies were in small selected populations and only four of these studies were controlled for potential confounders using multivariate analysis (4, 7, 9, 19). In keeping with our findings, some studies have also found no overall increase of placenta previa (7, 18), placental abruption (3, 9, 18), gestational diabetes (6, 11, 13, 15, 18), or preeclampsia (6). Although we found a large increase in odds of placenta previa restricted to women with exacerbations, and of thyroid disorder restricted to women with severe asthma, these did not show general trends with asthma severity and exacerbations, and it is possible that they were chance findings considering the large numbers of outcomes studied. Our general finding of an increased risk of hemorrhage was in agreement with four studies that reported similar or higher increased risks (1, 4, 10, 13) but in contrast with others (7, 9, 11, 15, 18).

Although it has been suggested that variations in previous studies may be related to differing asthma severity and management, we found no clear trends of associations between varying prepregnancy asthma severity or exacerbations and most obstetric complications. This can be particularly seen for the risks of antepartum and postpartum hemorrhage, which raises the possibility that women with asthma in general, whether or not their disease is currently active, may have persisting immunologic, hormonal, or other yet unknown physiologic differences compared with women without asthma. Two of the largest previous studies, of more than 11,000 and 43,000 women, respectively (9, 10), both found increased risks of hypertension and preeclampsia, which are in contrast to our results; however, their populations were derived from hospital register data with reported asthma prevalences of 0.5 and 0.43%, respectively, indicating that there was considerable underrecording of true asthma prevalence in their populations (20). The most striking finding in our study was a large increased risk of depression in pregnancy in women with asthma, which was larger in women with more severe asthma. To the authors' knowledge, this has not been previously investigated on a population level, and although the association of depression with pregnancy is well known, the finding that this may be more common in pregnant women with asthma warrants further investigation. One possible explanation is that having a chronic disease such as asthma during pregnancy may present added stress in a time when women are already at an increased risk of depression, and it is possible that being on higher levels of medications or having worse symptoms increases this stress further. An alternative explanation is potential ascertainment bias, because women with asthma visit their doctor more often and so have a greater opportunity to have depression recognized. Furthermore, primary care physicians in the United Kingdom are encouraged to look for depression among people with physical diseases. Screening for depression among people with long-term conditions is included as a quality indicator in the contract for general practitioners working in the U.K. National Health Service. Thus, there is scope for greater ascertainment of depression among women with asthma.

Most other studies, with the exception of two (1, 13), found an increased risk of caesarean section delivery (7, 9–11, 13, 15–18), but studies have not found increased risks of assisted delivery (1, 9, 17). Our finding of an increased risk of caesarean but not of assisted delivery for women with asthma may be explained by physician and patient concern over the safety of normal delivery rather than as a result of an asthma-related emergency. This could also be supported by our findings of higher increased risks of caesarean section in women with severe asthma and asthma exacerbations in the year before pregnancy. When using general practice data, it is important to consider that some of the associations found may reflect an increased tendency of doctors to ascertain some outcomes or take specific precautions for women with asthma because they see them more often. This will result in the risk estimates being inflated for women with asthma and may be an explanation for increased diagnoses of depression or the choice of delivering by caesarean section for women with asthma in general, regardless of the severity of their asthma.

Clinical Implications for Pregnant Women with Asthma

Our results provide reassuring evidence that the risks of most adverse pregnancy outcomes and obstetric complications are similar to those in women without asthma. We have found lower risks for major obstetric outcomes compared with some previous studies; however, some new questions have been raised that warrant further study. The risk of pregnancy ending in miscarriage may be higher in women with asthma and, with more severe asthma, the increased risks found for some obstetric com-

plications represented small differences in absolute risk. Greater severity of asthma and the occurrence of acute exacerbations in women with asthma are associated with modest increased risks of some obstetric complications. With the possible exception of increased vigilance in monitoring certain complications in pregnant women with asthma, our findings do not indicate a necessity to alter current practice of optimal pharmacologic management of asthma in women of child-bearing age in the general population.

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