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Early View

Original article

Effect of asthma exacerbation during pregnancy in women with asthma: A population-based cohort study

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Title page:

Title: Effect of asthma exacerbation during pregnancy in women with asthma: A population-based cohort study.

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Take home message:

Our study has shown women with asthma having asthma exacerbation during pregnancy have increased risk of adverse maternal and child health outcomes. Women with asthma during pregnancy require appropriate asthma management and follow-up.

Abstract:

The association between asthma exacerbation (AE) during pregnancy and adverse maternal and child health outcomes have not been appropriately investigated. Our objective was to determine the short- and long-term intergenerational effect of AE in pregnant women with asthma.

A population cohort study was conducted using data from the Ontario asthma surveillance system and population-level health administrative data. AE in pregnant women with asthma was defined as at least one of the following criteria: ≥ 5 physician visits, or 1 emergency department visit, or 1 hospital admission for asthma during pregnancy. Pregnancy complications, adverse perinatal outcomes, and early childhood respiratory disorders were identified using ICD codes 9th and 10th Revisions.

The cohort consisted of 103424 singleton pregnancies in women with asthma. AE in pregnant women with asthma was associated with higher odds of preeclampsia (OR 1.30; 95% CI 1.12, 1.51), and pregnancy induced hypertension (OR 1.17; 95% CI 1.02, 1.33); babies had higher odds of low birth weight (OR 1.14; 95% CI 1.00, 1.31), being pre-term (OR 1.14; 95% CI 1.01, 1.29), and congenital malformations (OR 1.21; 95% CI 1.05, 1.39). Children born to women with AE during pregnancy had elevated risk of asthma (OR 1.23; 95% CI 1.13, 1.33) and pneumonia (OR 1.12; 95% CI 1.03, 1.22) during first 5 years of life.

AE during pregnancy in women with asthma showed increased risk of pregnancy complications, adverse perinatal outcomes and early childhood respiratory disorders in

their children, indicating appropriate asthma management may reduce the risk of adverse health outcomes.

Background:

Asthma is the most common chronic disease encountered during pregnancy, occurring in 8-13% of pregnant women worldwide (1) . Nearly 40% of pregnant women decrease or stop taking asthma medications due to concerns regarding the safety of asthma medications (2,3) . Poorly controlled asthma may increase asthma severity and the risk of having asthma exacerbation (AE) during pregnancy (1,4–7) . Evidence has found that 1 in 3 women with asthma suffer from exacerbation during pregnancy (4,5) . The key priority in asthma management during pregnancy is maintenance of optimal asthma control.

Various factors may contribute to the development of asthma exacerbation during pregnancy, such as pre-existing severe asthma, non-adherence to controller medication, viral infections, obesity, parity, smoking, environmental smoke and outdoor air pollutants (8–11) . Additionally, risk factors related to health disparities such as specific ethnicity, low socioeconomic and immigrant status may also play a role (9,12) .

Asthma exacerbation during pregnancy has been found to be associated with adverse perinatal and pregnancy outcomes such as low birth weight, small-for-gestational age, pre-term delivery, congenital malformation, preeclampsia and perinatal mortality (1,5,8,11,13) . However, studies reporting these associations were small cohorts comparing asthmatic women with non-asthmatics during pregnancy.

Furthermore, studies using cross-sectional design have reported that AE during pregnancy can lead to increased risk of asthma, bronchiolitis, atopic dermatitis and allergic rhinitis in their children during early childhood (14–18) . To date, no study has longitudinally followed babies born to women with asthma experiencing AE during pregnancy and investigated the impact of AE on children's respiratory health during early childhood.

Considering the high incidence of asthma exacerbation during pregnancy and the tendency of women to stop taking asthma medication during pregnancy, it is important to examine the possible short and long-term impact of this dangerous health condition. Therefore, the objective of this study is to comprehensively evaluate the effect of AEs in pregnant women with asthma on maternal and child health in a diverse multi-ethnic population-based cohort.

Methods:

Data source and ethics consideration

Population-based data from the province of Ontario, Canada, were used for this study. Ontario has a universal, single-payer health-care system that covers all physician and hospital services for the province's 14 million residents. Five health administrative databases were used in this study: 1) the Ontario Health Insurance Plan (OHIP) database, which contains information on all fee-for-service billings for physician services rendered; 2) the National Ambulatory Care Reporting System database (NACRS), which contains data for hospital-based and community-based emergency and ambulatory care (e.g., day surgery and outpatient clinics); 3) the Ontario Registered

Persons Database (RPBD), which includes information on sex, date of birth and residence postal code; 4) The Mother-Baby (MOMBABY) database, which contains information on admission records for mothers and their babies was derived by linking inpatient records of delivering mothers and their newborns, collected by the Canadian Institute for Health Information, and 5) Ontario's Better Outcomes Registry and Network (BORN) database which collects data on every birth and young child in Ontario. The MOMBABY database was used to identify babies born to mothers with asthma exacerbation during pregnancy. The BORN database was used to identify the perinatal and respiratory health outcome of mothers and their children (19) .

Records in these databases were individually linked using Ontario residents' unique, encrypted health card numbers. This linkage protects individuals' identity while allowing for examination of residents' health service use across multiple health administrative databases. These health administrative databases are housed at ICES in Ontario, Canada. This study was approved by the research ethics board at The Hospital for Sick Children.

Study design and population

This is a longitudinal population-based cohort study where mother-baby pairs were identified from health administrative databases and their health outcomes studied from April 1, 2003 to March 31, 2012 (max follow-up date: March 31, 2015)

Mother Cohort: The mother cohort included women aged between 13-45 years with prevalent asthma during pregnancy who had at least 1 pregnancy resulted in a live or still birth between fiscal year (FY) 2006 and FY2012. Women with multiple births,

without OHIP coverage for period of 14 months prior to pregnancy, who are missing data on age, residence postal code and non-identifiable in the MOMBABY database were excluded.

Baby Cohort: Babies born to women with prevalent asthma during pregnancy were identified from the MOMBABY database and were followed from birth to 5 years of age. Still birth or babies who died before age 5 years were excluded from the cohort. We excluded multiple births, as the intrauterine physiology underlying maternal-fetal transmission differs between multiples and singletons and multiple pregnancies have a significant risk complications (13) .

Measures

Asthma Case Definition

The Ontario Asthma Surveillance Information System (OASIS) is a population-based, longitudinal surveillance system that uses health administrative data to identify and track individuals living with asthma in Ontario (20) . It uses a validated case definition of asthma to monitor its prevalence and incidence in the Ontario population. This case definition of at least 2 asthma physician visits within 2 consecutive years or at least 1 asthma hospitalization yielded 89% sensitivity and 72% specificity in children (aged 0–17 years) and 84% sensitivity and 76% specificity in adults (aged 18 years or over) (20–22) . Once entered into the database, patients remained part of the asthma population until they moved out of the province or died in order to be consistent with previous evidence indicating that asthma, once diagnosed, may remit but does not resolve (23,24).

Exposure: *Maternal asthma exacerbation (AE)*

The primary exposure was occurrence of asthma exacerbation during pregnancy. Currently there is no validated health administrative definition of AE. We used the modified version of a definition used by Blais et al (6,13) . We defined AE as at least one of the following conditions: GP visits for asthma ≥ 5 times; or 1 emergency department visit for asthma; or 1 hospital admission for asthma during the length of pregnancy.

Outcomes:

1) Maternal pregnancy-related complications: Pre-eclampsia, pregnancy induced hypertension (PIH) and maternal death were identified from the MOMBABY database.

2) Perinatal adverse outcomes: Outcomes identified in the babies include: low birth weight (LBW), small-for-gestational-age (SGA), preterm babies (PTB), congenital malformation (CM), transient tachypnea of the new born (TTN), respiratory distress syndrome (RDS).

3) *Early childhood respiratory disorders*: Incidence of respiratory health outcomes (allergy, wheeze, asthma, bronchiolitis, and pneumonia) during the first 5 years since birth were captured from the Ontario health administrative databases.

All maternal pregnancy-related complications, perinatal adverse and early childhood respiratory outcomes are defined by International Classification of Disease 9th and 10th Revisions (ICD-9 and ICD-10 codes) (see eTable 1, eTable 2 and eTable 3 in the supplement).

Covariates

We adjusted our analysis by a number of covariates that may be confounding the association between AE and health outcomes, including: mother's age, parity, maternal smoking during pregnancy, rural residence, and socio-economic status (SES). Socioeconomic status (SES) was determined using the Ontario Marginalization Index (ON-Marg) (25). On-Marg is a census-based, geographically derived index that consists of four domains, residential instability, material deprivation, ethnic concentration and dependency. Each domain is measured by quintiles where the 5th quintile reflects the greatest magnitude of marginalization (i.e., the most marginalized) and the 1st quintile reflects the least magnitude (26). Other covariates included baby's sex and comorbid conditions. Comorbid conditions were adjusted for using the Condensed Aggregated Diagnostic Groups (CADGs) that included cardiovascular disease, COPD, diabetes, hypertension, lung cancer, and non-lung cancers. CADGs are person-focused, diagnosis-based method of categorizing subjects' illnesses that are based on ICD codes (27) .We assessed potential effect modifiers (maternal age and maternal smoking) on the primary association investigated in this study (between perinatal outcomes/maternal pregnancy complication/ respiratory outcomes in children and maternal AE during pregnancy)(17) .

Statistical analysis

Descriptive statistics were performed to present the distribution of exposure variables, outcome variables, and covariates of the study. Chi square test for categorical variables and t-test for continuous variables was used to assess differences between women with asthma with and without AE during pregnancy. We also estimated the

proportion of all outcomes (perinatal, pregnancy complication and respiratory disorders) in women with asthma who did and did not have AE during pregnancy.

Association between AE in women with asthma (during pregnancy) and perinatal outcomes and pregnancy complications were investigated using logistic regression analysis with generalized estimating equation (GEE) for repeated measures (28) . The GEE models take into account that a women could contribute more than 1 pregnancy to the analysis by estimating the correlation between consecutive pregnancies (6). All odds ratios (OR) were presented with 95% confidence intervals (CI) after adjusting for potential confounding variables. Separate multivariable regression models were developed for each of the pregnancy and perinatal outcome.

Poisson regression analysis with generalized estimating equation (GEE) for repeated measures was performed to estimate the risk of early childhood respiratory conditions and AE in women with asthma during pregnancy. The number of observed days for each child was used as the offset variable. Estimates of relative risk (RR) with 95% CI are reported. Each respiratory outcome was modelled in a separate Poisson regression analysis.

Effect modification was assessed by including interaction terms between relevant risk factors (maternal age and smoking) and AE (29) . We considered an interaction term to be significant if it had a p value of <0.3. Only significant interaction terms were considered to be included in the models.

All analyses were carried out using SAS Enterprise guide 6.1 (SAS Institute Inc., Cary, NC). Control of confounding and reporting of results was performed using guidance given in *Lederer et al 2019*.

Results:

The cohort consisted of 103424 singleton pregnancies in 58,524 women with asthma. A total of 4,455 pregnancies had AE in 2663 women with asthma.

Table 1 depicts the characteristics of pregnancies with asthma exacerbation in women with asthma (n= 103424). Significantly greater proportions of women with AE were aged between 34 - 45 years (17.8%vs.16.7 %, p = 0.002), smoked during pregnancy (25.6% vs.19.1%, p = <0.001) and were in the highest quintile (most deprived) of the material deprivation (22.3% vs. 18.1%, p = <0.001) and residential instability (21.4% vs.17.0%, p = <0.001) dimension of the ON-Marg index.

Maternal-related complications

Figure 1 shows pregnancy complication in women with asthma who did and did not have AE during pregnancy. A significantly greater proportion of pregnancies with AE had pre-eclampsia (5.32% vs. 3.84%, p<0.001), and PIH (7%% 5.37vs. p<0.001). Table 2 and Figure 2 show the results of the multi-variable logistic regression model adjusted for potential confounders. Compared to women with asthma who did not have AE during pregnancy, adjusted OR for pre-eclampsia was 1.30 (95% CI 1.12, 1.51; p<0.001) and for PIH 1.17(95%CI 1.02, 1.33; p0.022) in women with asthma having AE during pregnancy.

Adverse perinatal outcomes

Figure 1 shows perinatal outcomes in women with asthma who did and did not have AE during pregnancy. Babies born to mothers who experienced AE during pregnancy had higher proportion of adverse perinatal outcomes: LBW (6.76% vs. 5.28%, p<0.001), SGA (2.45%vs. 1.89%, p=0.008), pre-term baby (8.15% vs. 6.66%, p<0.001), and congenital malformation (6.2%vs. 4.97%, p<0.001). After adjusting for confounding and testing of effect modification, Table 2 and Figure 2 show compared to women with asthma who did not have AE during pregnancy, the adjusted OR for LBW was 1.14 (95%CI 1.00, 1.31; p=0.049), for pre-term birth 1.14, (95%CI 1.01, 1.29; p=0.036), and for CM 1.21(95% CI 1.05, 1.39; p=0.007) in women with asthma having AE during pregnancy.

Early childhood respiratory disorders

Slightly higher proportion of children with allergy (16.93% vs. 15.72%, p=0.051), asthma (37.77% vs. 31.39%, p=<0.001), bronchiolitis (39.72% vs. 39.05%, p=0.382) and pneumonia (24.38% vs. 21.69%, p=<0.001) were born to women with asthma having AE during pregnancy. In case of wheeze, there was a higher proportion in children born to non-AE women with asthma (83.19% vs. 84.72%). The adjusted multivariable Poisson regression showed elevated risk ratios for asthma (RR=1.23, 95%CI 1.13, 1.33; p<0.001) and pneumonia (RR=1.12, 95%CI 1.03, 1.22; p<0.006) in women with asthma having AE during pregnancy (Table 3).

For all outcome assessment, no significant interactions between maternal age and smoking was identified with AE.

Discussion:

Adverse perinatal outcomes and pregnancy complications

From our large cohort study including over 100,000 pregnancies we have found the odds of pre-eclampsia was 30% higher and the odds of pregnancy-induced hypertension was 17% higher in women with asthma who experienced AE during pregnancy. In babies born to women with asthma who experienced AE during pregnancy, the odds of being LBW and preterm was 14% higher and the odds of having congenital malformation was 21% higher. Our study did not identify any association with SGA, TTN and RDS.

Our results are consistent with findings from a previous systematic review where pregnant women with AE were compared to pregnant women without AE for pregnancy complications and adverse perinatal outcomes (1,2,8,30) . However, most of the studies in the review were small cohorts with varying definitions of asthma severity and comparison groups (e.g. some had compared asthmatic women with non-asthmatics). Our study is the first to use population level data to measure the association between AE during pregnancy and adverse perinatal outcomes and pregnancy complications. Furthermore, our study has compared women with asthma who experienced exacerbation during pregnancy to those who have asthma but did not have exacerbation during pregnancy. Thus, our results denote the impact of AE during pregnancy, as opposed to the impact of asthma.

Effect on respiratory health of children born to mothers experiencing AE during pregnancy

In the second part of our study, we aimed to identify the long-term impact of AE during pregnancy. We found that children born to women with asthma having AE during pregnancy had 23% higher risk of developing asthma before 5 years of age. Previous studies have reported children whose mothers had AE during pregnancy, had increased risk of developing asthma during early childhood (15,18) . These studies were performed using population level data and similar to our study had compared asthmatic women with AE during pregnancy to those without AE. Hence, our results corroborate with previous evidence. However, our study is the first to show the intergenerational impact of AE during pregnancy by following babies born to women with asthma up to their 5 years of age and evaluating the impact of AE during pregnancy on early childhood respiratory health.

Our study also identified children born to women with asthma having AE during pregnancy to be at 12% higher risk of having pneumonia during first 5 years of life. This finding has not been reported in previous studies. However, previous evidence has shown children of mothers with uncontrolled asthma during pregnancy to be more at risk for other respiratory infections such as bronchiolitis and allergic rhinitis (14,17) . Hence, further research is needed to ascertain this association in the pediatric population.

The strengths of this study include the prospective longitudinal design and inclusion of 58,524 mother-child pairs and over 100,000 pregnancies. Following babies (born to women with asthma experiencing AE during pregnancy) up to their 5 years of

age, has allowed to demonstrate the intergenerational effect of AE during pregnancy. The data linkage across multiple administrative databases ensures that the assessment of outcome is free from individual recall bias. We used validated case definition of asthma as well as used ICD codes to ascertain other health outcomes. Our risk estimates were adjusted for a multitude of potential confounders (eTable 4 and 5) including maternal smoking and comorbidities, however, residual confounding from unmeasured confounders may still exist.

There are some limitations of our study. Currently there are no validated algorithm for AE. We defined AE based on a modified version of the algorithm used by Blais et al which includes - 1 filled prescription of oral corticosteroids; or 1 emergency department visit for asthma; or 1 hospital admission for asthma during the length of pregnancy (13) . Validation of our algorithm is beyond the scope of our study.

Using ≥5 GP visits as a criteria for AE in women with asthma, may have the potential to misclassify women being well-monitored to those with AE. However, previous evidence has shown ≥ 4 outpatient visits with an asthma code to be a flag for persistent asthma (31). Hence by using ≥5 GP visits as a criteria of AE, we have reduced the potential for misclassification. The higher level of GP visit for asthma is highly likely for AE or poorly controlled asthma than diligent monitoring. Future study is needed to validate this case definition to establish its sensitivity and specificity.

We did not categorize asthma exacerbation according to its severity. Based on the work performed by Blais et al. , we expect our sample to include moderate to severe asthma exacerbation groups (13). Had we adjusted for severity, our results would not have been grossly different, the magnitude of our findings may have differed.

The use of asthma medications, such as oral corticosteroids, during pregnancy may contribute to the development of these adverse outcomes (32–34) . Due to lack of medication data in the Ontario health administrative databases we were unable to incorporate the effect of asthma medication on perinatal and pregnancy outcomes. However, a severe asthma attack likely presents more of a risk to the fetus than the use of asthma medications because it can provoke maternal hypoxia which, in addition to decreased placental blood flow, will reduce oxygen supply to the fetus (1,8,35).

Conclusion:

Our population-based cohort study identified the detrimental effects of AE during pregnancy. In addition, using a prospective design this study has captured the long-term intergenerational effect of AE during pregnancy by following the same babies up to 5 years of age. Targeting women with asthma during pregnancy and ensuring appropriate asthma management and postpartum follow-up may help to reduce the risk of pregnancy complications, adverse perinatal outcomes and early childhood respiratory disorders.

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conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

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Table 1: Characteristics of pregnancies with and without AE in women with asthma (n= 103424).

	No AE (n=98969)	**AE (n=4455)**
Maternal characteristics, n (%)		
Age category		
13-17	3798 (3.84)	206 (4.62)
18-34	78678 (79.50)	3454 (77.53)
34-45[a]	16493 (16.66)	795 (17.85)
Parity, median (range)	1 (0 – 18)	1 (0-11)
Smoking during pregnancy, **n (%)**[a]	16868 (19.19)	973 (25.59)
Rurality, **n (%)** [a]	11553 (11.70)	610 (13.70)
ON-MARG index, **n (%)**		
Dependency quintile		
1	27783 (28.07)	1240 (27.83)
2	23039 (23.28)	1013 (22.74)
3	18569 (18.76)	857 (19.24)
4	15292 (15.45)	661 (14.84)
5	13042 (13.18)	629 (14.12)
Material deprivation quintile		
1	25250 (25.51)	1004 (22.54)
2	19983 (20.19)	862 (19.35)
3	18213 (18.40)	783 (17.58)
4	16407 (16.58)	756 (16.97)
5[a]	17872 (18.06)	995 (22.33)

Ethnic concentration quintile		
1	10760(10.87)	470(10.55)
2	15245(15.40)	678(15.22)
3	17856(18.04)	815(18.29)
4	22345(22.58)	995(22.33)
5	31519(31.85)	1442(32.37)
Residential instability quintile		
1	22643(22.88)	808(18.14)
2	21570(21.79)	863(19.37)
3	16556(16.73)	777(17.44)
4[a]	20132(20.34)	999(22.42)
5[a]	16824(17.00)	953(21.39)
Baby characteristics		
Sex, **n (%)**		
Female	47893 (48.93)	2129 (48.36)
Male	49993 (51.07)	2273 (51.64)
Birthweight, gms median (range)	3405 (276, 8639)	3366.50 (329, 5605)

AE: Asthma exacerbation; ON-MARG index: Ontario Marginalization Index
[a]$p < 0.05$

Table 2: Risk associated with pregnancy complications and adverse perinatal outcomes in women with asthma, experiencing AE during pregnancy.

Risk factors	Pregnancy complications		Adverse perinatal outcomes		
	Pre-eclampsia	PIH	LBW	PTB	CM
	OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value
Asthma exacerbation (AE) during pregnancy					
	1.30 (1.12,1.51), <0.001	1.17 (1.02,1.33), 0.022	1.14 (1.00, 1.31), 0.049	1.14 (1.01, 1.29), 0.036	1.21 (1.05, 1.39), 0.007

AE: asthma exacerbation; OR: Odds ratio; CI: Confidence interval

PIH: Pregnancy induced hypertension

LBW: Low birth weight; PTB: Pre-term birth; CM: Congenital malformation

*Adjusted covariates

Pregnancy complications: maternal age, parity, maternal smoking, Ontario Marginalization Indices (residential instability, material deprivation, ethnic concentration and dependency), Collapsed Ambulatory Diagnostic Groups (CADGs): Acute: minor, Acute: Major, Likely to Recur, Chronic Medical: Unstable, Chronic Medical: Stable, Chronic Specialty: Stable, Eye/Dental, Chronic Specialty: Unstable, Psychosocial/Psychophysiologic, and Prevention/Administrative.

Adverse perinatal outcomes: maternal age, parity, maternal smoking, sex of child, Ontario Marginalization indices (residential instability, material deprivation, ethnic concentration and dependency).

Table 3: Risk associated with developing respiratory disorders in children of women with asthma, experiencing AE during pregnancy.

Outcomes	N	RR (95% CI)	p-value	RR (95% CI)	p-value
		Unadjusted		Adjusted	
Allergy[a]	15788	1.09 (1.00, 1.18)	0.0506	1.06 (0.96, 1.16)	0.2453
Wheeze[a]	83902	0.98 (0.94, 1.01)	0.1949	1.02 (0.98, 1.06)	0.3438
Asthma[b]	31536	1.36 (1.26, 1.47)	<.0001	1.23 (1.13, 1.33)	<.0001
Bronchiolitis[c]	38925	1.04 (0.98, 1.10)	0.2164	1.03 (0.96, 1.10)	0.4002
Pneumonia[c]	21723	1.16 (1.08, 1.25)	<.0001	1.12 (1.03, 1.22)	0.0056

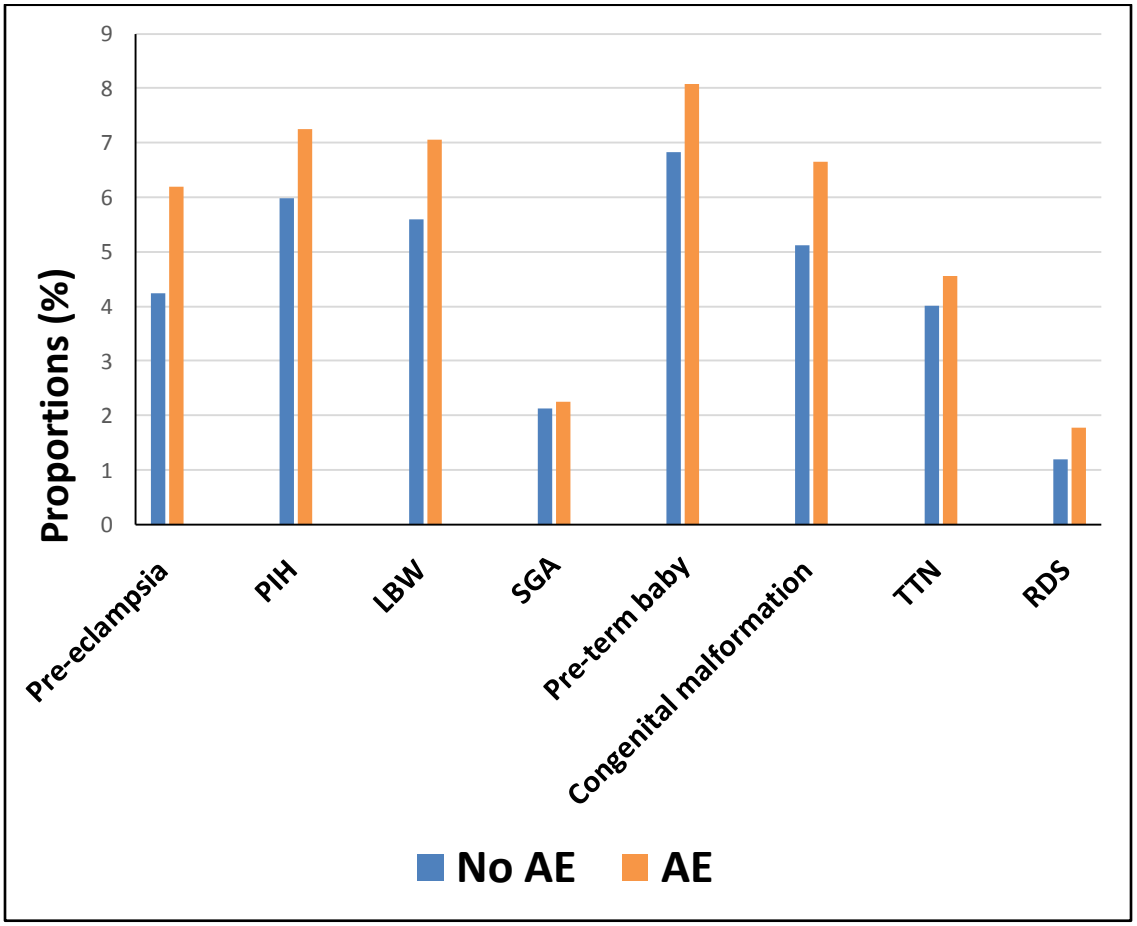
AE: asthma exacerbation; RR: Relative risk; CI: Confidence interval

[a]***adjusted for:*** sex of the baby, LBW baby, SGA baby, preterm baby, APGAR score in 1 minute, admitted to ICU after birth, history of TTN, history of RDS, maternal age at delivery, maternal smoking during pregnancy, parity, history of maternal asthma, rurality, dependency quintile, material deprivation quintile, ethnic concentration quintile, residential instability quintile, maternal pre-eclampsia during pregnancy, and maternal PIH during pregnancy

[b]***adjusted for:*** sex of the baby, LBW baby, preterm baby, APGAR score in 1 minute, admitted to ICU after birth, history of TTN, history of RDS, parity, history of maternal asthma, rurality, material deprivation quintile, ethnic concentration quintile, residential instability quintile

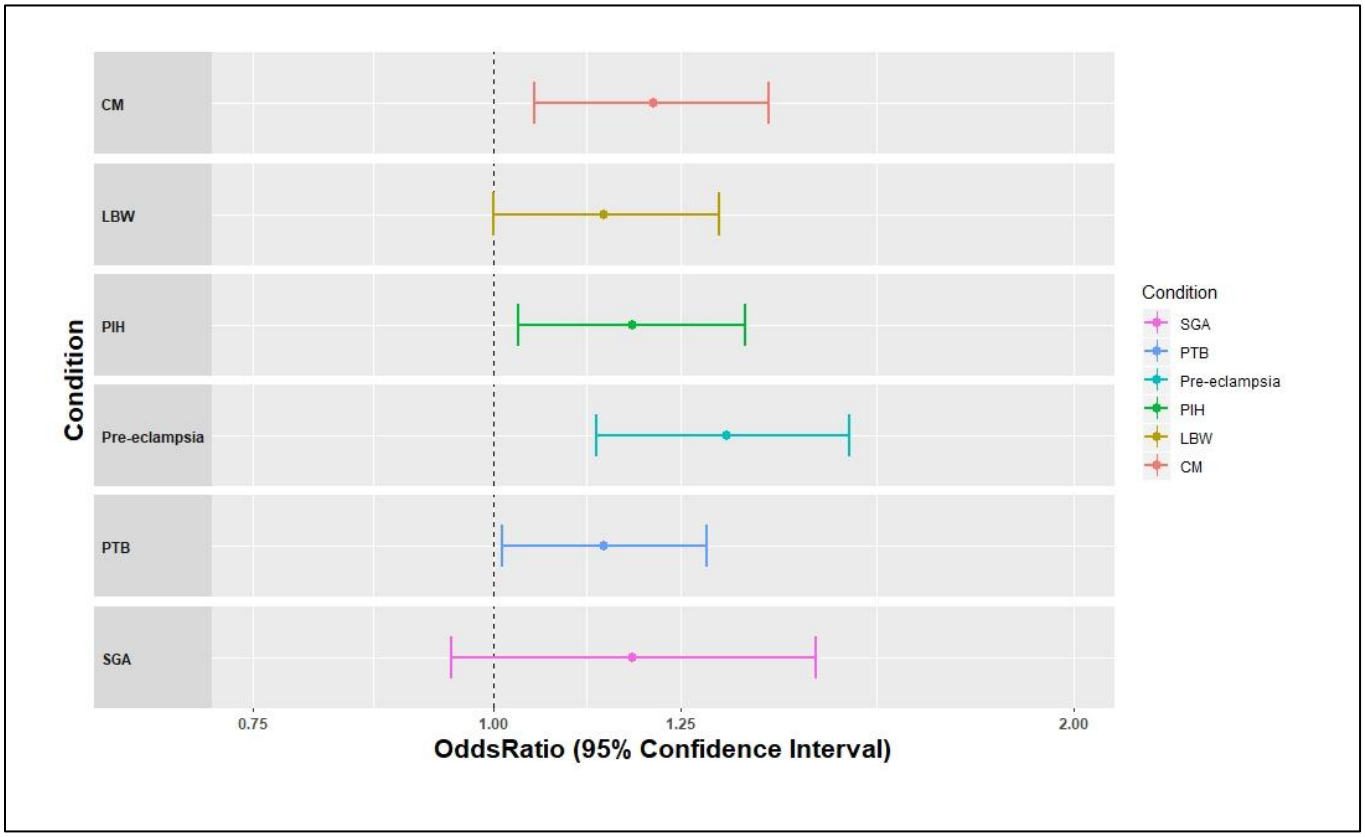
[c] ***adjusted for:*** sex of the baby, LBW baby, preterm baby, admitted to ICU after birth, maternal age at delivery, smoking during pregnancy, parity, history of maternal asthma, rurality, dependency quintile, deprivation quintile, ethnic concentration quintile, residential instability quintile

Figure 1: Proportion of adverse perinatal outcomes and pregnancy complications in women with asthma who did and did not have AE during pregnancy.



PIH: Pregnancy induced hypertension; LBW: Low birth weight; SGA: Small-for-gestational age; TTN: Transient tachypnoea of the newborn; RDS: Respiratory distress syndrome

Figure 2: Risk of developing pregnancy complications and adverse perinatal outcomes in women with asthma having AE during pregnancy.



PIH: Pregnancy induced hypertension; LBW: Low birth weight; SGA: Small-for-gestational age; PTB: Pre-term birth; CM: Congenital malformation

eTable 1: Definition and International Classification of Disease (ICD) codes for pregnancy complications

Pregnancy Complications	Definition	ICD diagnosis codes	
		9	10 CA
Pre-eclampsia	It is a pregnancy-specific disease characterized by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features. *(Steegers et al. Lancet 2010; 376: 631–44)*	642	O14.0
Pregnancy induced hypertension (PIH)	Hypertension in pregnancy is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. According to the levels of BP, hypertension is mild if SBP is measured between 140–149 mmHg and DBP 90–99 mmHg, moderate if SBP is 150–159 and DBP 100–109 mmHg and severe if SBP is equal or greater than 160 mmHg and DBP than 110 mmHg. *(Antza et al Metabolism 2018; 86: 102-111)*	6423	O13

eTable 2: Definition and International Classification of Disease (ICD) codes for adverse perinatal outcomes.

Adverse Perinatal Outcomes	Definition	ICD diagnosis codes	
		9	10 CA
Low birth weight (LBW)	Low birthweight has been defined as weight at birth of less than 2,500 grams (5.5 pounds). (*United Nations Children's Fund and World Health Organization, Low Birthweight: Country, regional and global estimates. UNICEF, New York, 2004.URL: https://www.unicef.org/publications/index_24840.html*	765, V21	P07.1, P07.0
Small-for-gestational age (SGA)	Babies with birthweight below the 10th percentile for the gestational age. *(WHO expert committee on physical status: the use and interpretation of anthropometry physical status: report of a WHO expert committee. Geneva 1995. URL: https://apps.who.int/iris/handle/10665/37003*	764, 764	P05.1, P05.9
Preterm birth (PTB)	Babies born alive before 37 weeks of pregnancy are completed. (*United Nations Children's Fund and World Health Organization, Low Birthweight: Country, regional and global estimates. UNICEF, New York, 2004.URL: https://www.unicef.org/publications/index_24840.html*	644	O60.00
Congenital malformation (CM)	A congenital malformation is a congenital physical anomaly that is a structural defect perceived as a problem. A typical combination of malformations affecting more than one body part is referred to as a malformation syndrome. *(Demissie et al. Am J Respir Crit Care Med 1998; 158:1091–1095)*	740 - 759	Q00 - Q99

Transient tachypnea of the new born (TTN)	Transient tachypnea is most common after term cesarean delivery and characterized by the early onset of tachypnea, sometimes with retractions, or expiratory grunting and, occasionally, cyanosis that is relieved by minimal oxygen supplementation (<40%). *(Marcdante, K J, and Kliegman RM. Nelson Essentials of Pediatrics. 7th ed., Elsevier Saunders, 1990.)*	7706	P22.1
Respiratory distress syndrome (RDS)	Respiratory distress syndrome occurs primarily in premature infants caused by deficiency of surfactant, a lipoprotein which reduces surface tension within the lung. *(Marcdante, K J, and Kliegman RM. Nelson Essentials of Pediatrics. 7th ed., Elsevier Saunders, 1990.)*	769	P22.0

eTable 3: International Classification of Disease (ICD) codes for child respiratory outcomes

Child Respiratory Outcomes	ICD diagnosis codes	
	9	10 CA
Allergies	9953, 4770, 4778, 4771, 4772, 4779	T78.4, J30.1 , J30.2 , J30.3, J30.4
Wheeze/cough	78607	R06.2
Asthma	493	J45, J46, J45.01
Bronchiolitis	466	J21
Pneumonia	481,486, 485, 4800, 4801, 4802, 4808, 4822, 4830, 4831, 48232, 48282, 48283, 48284	J10.0, J12.0, J12.1, J12.2, J12.8, J13, J14, J15.3, J15.5, J15.6, J15.7, J16.0, J18.0, J18.1, J18.2, J18.9

eTable 4: Risk factors associated with pregnancy complications and adverse perinatal outcomes in women with asthma having asthma exacerbation during pregnancy.

Risk factors		Pregnancy complications		Adverse perinatal outcomes		
		Pre-eclampsia	PIH	LBW	PTB	CM
		OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value	OR (95%CI), p value
Asthma exacerbation (AE) during pregnancy						
		1.30(1.12,1.51), <0.001	1.17(1.02,1.33), 0.022	1.14 (1.00, 1.31), 0.049	1.14 (1.01, 1.29), 0.036	1.21(1.05, 1.39), 0.007
Age of mother at birth (in years)						
	13-17	0.58(0.47,0.72), <0.001	0.63(053,0.76), <0.001	0.88 (0.75,1.04), 0.137	0.81 (0.69, 0.95), 0.011	0.82 (0.68, 0.98), 0.03
	18-34	ref	ref	ref	ref	ref
	35-45	1.27(1.16,1.39), <0.001	1.28(1.18,1.38), <0.001	1.16 (1.07,1.26), <0.001	1.15 (1.07, 1.24), 0.001	1.14 (1.05, 1.24), <0.001
Maternal smoking during pregnancy						
		-	-	1.85 (1.72, 1.99), <0.001	1.33 (1.24, 1.42), <0.001	0.97 (0.89, 1.05), 0.438
Parity						
	Nulliparous	2.30(1.94,2.72), <0.001	1.94(1.70,2.22), <.001	1.10 (0.24, 1.24), 0.114	0.86 (0.78, 0.96), 0.006	1.14 (0.99 - 1.29), 0.05
	1-2	ref	ref	ref	ref	ref
	≥3	0.89(0.75,1.05), 0.164	1.09(0.95,1.24), 0.223	1.34(1.19, 1.50), <0.001	1.38 (1.24, 1.52), <0.001	1.03 (0.91 - 1.17), 0.622
Baby sex						
	Male	-	-	ref	ref	ref
	Female	-	-	1.04 (1.01, 1.07),	0.91 (0.88, 0.93),	0.81(0.78, 0.83),

				0.004	<0.001	<0.001
Material deprivation quintile						
	1 (least)	0.84(0.74,0.95), 0.008	0.95(0.85,1.06), 0.382	0.83 (0.74, 0.93), 0.002	0.91 (0.82, 1.00), 0.065	0.96 (0.86 - 1.07), 0.484
	2	0.83(0.73,0.94), 0.004	0.89(0.79,0.99), 0.039	0.83 (0.74, 0.93), 0.001	0.93 (0.84, 1.03), 0.159	0.87 (0.78, 0.97), 0.016
	3	0.87(0.77,0.98), 0.028	0.92(0.83,1.02), 0.132	0.91 (0.82, 1.02), 0.098	0.91 (0.83, 1.00), 0.064	0.89 (0.80 - 0.99), 0.044
	4	0.88(0.78,0.10), 0.049	0.94(0.84,1.04), 0.218	0.94 (0.85, 1.04), 0.214	0.96 (0.88, 1.05), 0.386	0.99 (0.90, 1.11), 0.988
	5 (most)	ref	ref	ref	ref	ref
Ethnic diversity quintile						
	1 (least)	1.43(1.24,1.64), <0.001	1.46(1.30,1.65), <0.001	0.73 (0.64, 0.84), <0.001	0.86 (0.76, 0.96), 0.008	1.12 (0.99, 1.27), 0.073
	2	1.41(1.25,1.60), <0.001	1.26(1.13,1.39), 0.001	0.84 (0.75, 0.93), <0.001	1.00 (0.91, 1.10), 0.930	1.21 (1.09, 1.34), <0.001
	3	1.40(1.25,1.55), <0.001	1.23(1.12,1.35), 0.001	0.79 (0.72, 0.87), <0.001	0.89 (0.82, 0.98), 0.012	1.06 (0.97, 1.17), 0.202
	4	1.32(1.20,1.45), <0.001	1.20(1.11,1.31), <0.001	0.80 (0.74, 0.87), <0.001	0.91 (0.84, 0.98), 0.014	1.06 (0.97, 1.15), 0.194
	5 (most)	ref	ref	ref	ref	ref

OR: Odds ratio; CI: Confidence interval

PIH: Pregnancy induced hypertension

LBW: Low birth weight; PTB: Pre-term birth; CM: Congenital malformation

eTable 5: Risk factors significantly associated with developing respiratory disorders in children of women with asthma having AE during pregnancy

		Asthma	Pneumonia
		RR (95% CI), p value	RR (95% CI), p value
Asthma exacerbation (AE) during pregnancy			
		1.23 (1.13, 1.33), <0.001	1.12 (1.03, 1.22), 0.006
Baby sex			
	Male	ref	ref
	Female	0.82 (0.80, 0.83), <0.001	0.93 (0.91, 0.95), <0.001
LBW baby		1.30 (1.18, 1.42), <0.001	1.24 (1.13, 1.36), <0.001
Preterm baby		1.15 (1.06, 1.25), 0.001	1.14 (1.04, 1.25), 0.005
Baby was in ICU after birth		1.13 (1.06, 1.20), <0.001	1.27 (1.20, 1.35), <0.001
Baby TTN		1.24 (1.13, 1.36), <0.001	-
Baby RDS		1.38 (1.19, 1.60), <0.001	-
Age of mother at birth (in years)			
	13-17	-	1.08 (0.97, 1.21), 0.168
	18-34	ref	ref
	35-45	-	0.91 (0.86, 0.95), <0.001
Maternal history of asthma		1.16 (1.12, 1.21), <0.001	1.05 (1.01, 1.09), 0.019
Rurality		0.76 (0.71, 0.82), <0.001	1.19 (1.13, 1.26), <0.001
Maternal dependency quintile			
	1	-	0.86 (0.74, 1.01), 0.071
	2	-	0.83 (0.71, 0.97), 0.019

	3	-	0.84 (0.72, 0.98), 0.032
	4	-	0.87 (0.74, 1.02), 0.079
	5	ref	ref
Maternal ethnic diversity quintile			
	1	0.75 (0.64, 0.89), 0.001	-
	2	0.78 (0.66, 0.93), 0.004	-
	3	0.82 (0.69, 0.96), 0.016	-
	4	0.87 (0.74, 1.03), 0.103	-
	5	ref	ref
Maternal residential instability quintile			
	1	1.14 (1.08, 1.20), <0.001	-
	2	1.12 (1.05, 1.18), <0.001	-
	3	1.11 (1.05, 1.19), <0.001	-
	4	1.07 (1.01, 1.13), 0.030	-
	5	ref	ref

RR: Relative risk; CI: Confidence interval