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Asthma during Pregnancy in a Population-Based Study - Pregnancy Complications and Adverse Perinatal Outcomes

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Abstract

Background: Asthma is one of the most common chronic diseases, and prevalence, severity and medication may have an effect on pregnancy. We examined maternal asthma, asthma severity and control in relation to pregnancy complications, labour characteristics and perinatal outcomes.

Methods: We retrieved data on all singleton births from July 1, 2006 to December 31, 2009, and prescribed drugs and physician-diagnosed asthma on the same women from multiple Swedish registers. The associations were estimated with logistic regression.

Results: In total, 266 045 women gave birth to 284 214 singletons during the study period. Maternal asthma was noted in 26 586 (9.4%) pregnancies. There was an association between maternal asthma and increased risks of pregnancy complications including preeclampsia or eclampsia (adjusted OR 1.15; 95% CI 1.06–1.24) and premature contractions (adj OR 1.52; 95% CI 1.29–1.80). There was also a significant association between maternal asthma and emergency caesarean section (adj OR 1.29; 95% CI 1.23–1.34), low birth weight, and small for gestational age (adj OR 1.23; 95% CI 1.13–1.33). The risk of adverse outcomes such as low birth weight increased with increasing asthma severity. For women with uncontrolled compared to those with controlled asthma the results for adverse outcomes were inconsistent displaying both increased and decreased OR for some outcomes.

Conclusion: Maternal asthma is associated with a number of serious pregnancy complications and adverse perinatal outcomes. Some complications are even more likely with increased asthma severity. With greater awareness and proper management, outcomes would most likely improve.

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Data is available from third party; the Swedish National Board of Health and Welfare and Statistics Sweden. According to Swedish law, the authors are not able to share the register data used in this study with other researchers. Any researcher interested in obtaining the data used can do so by formally applying to the Swedish National Board of Health and Welfare and Statistics Sweden after obtaining an ethical permission from a Regional Ethical Review board in Sweden.

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Introduction

Asthma is one of the most common chronic diseases with reported prevalence between 3.7 and 8.4% [1,2]. Asthma symptoms may increase during pregnancy which can be attributable either to worsening of asthma due to the pregnancy itself or inadequate medication [3,4]. Maternal asthma has been associated with an increased risk for pregnancy complications such as preeclampsia, gestational diabetes, premature contractions and premature ruptures of membranes [5–8]. Maternal asthma has also been associated with an increased prevalence of labour characteristics including caesarean section and placental abruption [9–12], or perinatal outcomes such as low birth weight, prematurity and small for gestational age (SGA) [6,12–15] but studies are also non-consistent [2,7,16].

According to GINA (Global Initiative for Asthma) guidelines [17], asthma can be classified into mild, moderate and severe and symptoms should be treated with medication in a step-wise

approach to obtain asthma control. Mild and moderate well-controlled asthma is generally associated with uncomplicated pregnancy and delivery [8]. More importantly, severe asthma and poor asthma control seem to increase the risk of preterm delivery, low birth weight and small for gestational age (SGA) [18]. Yet, not all studies have reported increased risks of perinatal complications with severe asthma and poor control. A recent meta-analysis suggested that this discrepancy might be caused by variation in study size and that participation in smaller prospective studies is associated with better disease control and therefore better outcomes [19]. It is of great importance that midwives and obstetricians identify pregnant women at risk of adverse outcomes due to asthma. Thus, there is a call for larger studies to assess the effect of maternal asthma, severity and control on pregnancy complications, labour and perinatal outcomes.

Findings on the effect of maternal asthma on pregnancy and delivery outcomes in population-based cohorts compiled from registers offers many advantages including powerful assessment of the association between asthma in pregnant women and pregnancy complications or adverse outcomes, with control for important confounders and the effect of medication usage. By using information on asthma diagnosis from different sources and prescribed drugs as a proxy for disease it is possible to obtain objective measures of exposure. Indices developed to assess the severity and control of asthma can be used in epidemiological studies [20,21].

The principal aim of this study was to assess possible associations between maternal asthma, pregnancy and labour characteristics and adverse perinatal outcomes. We also aimed to assess the effect of asthma severity and control on pregnancy complications and perinatal outcomes.

Materials and Methods

Study design and population

The Swedish National Board of Health and Welfare holds a number of registers covering health information. The universal use of the Personal Identity Number (PIN), a unique identifier for each resident, enables unambiguous linkage to these registers and those held by Statistics Sweden [22]. We conducted a population-based cohort study using the four Swedish national registers held by the Swedish National Board of Health and Welfare and Statistics Sweden.

All women in Sweden who started their pregnancy after July 1 2006, bore singletons and gave birth at the latest 31 December 2009 were identified through the Medical Birth Register, which includes data on pregnancy and perinatal characteristics for approximately 99% of all births, after pregnancy week 22, in Sweden since 1973 [23]. The cohort was linked to the Prescribed Drug Register which contains all prescribed drugs dispensed at pharmacies in Sweden since July 1, 2005 [24], the National Patient Register which covers all in-patient care in Sweden from 1987 and 75% of all outpatient visits since 2001. Information on socioeconomic status including cohabitation and level of education was retrieved from the Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym), held by Statistics Sweden.

We included only singletons since multiple pregnancies exhibit many different characteristics compared to singletons.

Variables

Maternal characteristics. Maternal age and body mass index (BMI in kg/m^2), calculated from height and weight, were retrieved from the Medical Birth Register. Other background characteristics from the same source were parity, smoking, country of birth, cohabitation. Variables on maternal age and parity were recorded at delivery whereas maternal smoking habits, height and weight were registered at the first visit to the antenatal-care clinic in week 8–12. From LISA we collected information on marital status and highest level of maternal education at start of pregnancy.

Maternal asthma – diagnosis and medication. We used multiple registers to identify individuals with asthma in the study population. In the Medical Birth Register, a tick-box for self-reported asthma/lung disease ever is indicated by the midwife at antenatal care admission in early pregnancy. From the National Patient Register we obtained information on specialist care visits with a recently validated recorded diagnosis of asthma (ICD-10 codes J45, J46) twelve months before and during pregnancy [25]. Information on dispensed asthma medication before and during pregnancy was obtained from ATC-codes (Anatomical Therapeutic Chemical Classification) R03 (inhaled corticosteroids (ICS), short-acting β2-agonists (SABA), long-acting β2-agonists (LABA), leukotriene receptor antagonist (LTRA), anticholinergic inhalers, sodium chromoglycate, theophylline and omalizumab) and H02 (oral corticosteroids) in the Prescribed Drug Register. Having had asthma medication dispensed at least twice during the year before pregnancy until birth date was used as a proxy for an asthma diagnosis. We excluded oral β2-agonists (ATC code R03CC) since this is not only prescribed for asthma but sometimes for premature contractions. Our main exposure was asthma recorded in any of the three registers the Medical Birth Register, the National Patient Register or the Prescribed Drug Register.

In order to assess usage of asthma medication during different pregnancy trimesters, midwife reports were extracted from the Medical Birth Register along with gestational week of medication start and discontinuation.

We defined asthma severity and control based on medication use in the Prescribed Drug Register twelve months prior to pregnancy modified from Firoozi et al [21]. Average daily dose of ICS, SABA and two prescriptions per year of LABA, theophylline, and LTRA, along with asthma diagnoses in the National Patient Register inpatient part [26] and/or filled prescription of an oral corticosteroid over 12 months were used to categorize the mothers into mild or moderate/severe asthma that could be either controlled or uncontrolled, Appendix S1. The severity index was modified by changing the number of filled prescriptions for LABA, theophylline and LTRA from six to two over a 12 months period for adhering more to local prescription patterns.

Outcomes. All the outcome variables were collected from the Medical Birth Register. Based on pregnancy and delivery ICD-10 codes recorded we could collect information on preeclampsia/eclampsia (ICD-10: O14–15), gestational diabetes (ICD-10: O24), haemorrhage during pregnancy (ICD-10: O46), premature contractions (ICD-10: O47) premature rupture of membranes, PROM (ICD-10: O42) and placental abruption (ICD-10: O45).

We also included the following labour information: dystocia during labour, induced/spontaneous onset of labour, caesarean section (elective or emergency caesarean section prior to onset of labour, or emergency CS after onset of labour) and vaginal instrumental delivery (ICD-10-codes O62, O66.5, O81, O82 for forceps or vacuum extraction). Based on these, delivery mode was categorized as: 1) Vaginal, non-instrumental delivery, 2) Elective caesarean (before start of labour), 3) Vaginal instrumental delivery and 4) Emergency caesarean section (prior to or after start of labour).

For birth outcomes and post-partum characteristics we used data on birth weight, gestational age, small (SGA)/large (LGA) for

gestational age (birth weight >2 standard deviations below or above reference curve for children of similar gestational age) [27], Apgar at 5 minutes, information on haemorrhage after delivery (ICD-10: O72), and asphyxia/hypoxia (ICD-10: P20–P21).

Statistical analysis

We used logistic and multinomial logistic regression analysis to estimate odds ratios (OR) as the measure of association, with 95% confidence intervals (CI) for the outcomes in relation to asthma in any of the three registers as well as asthma medication in the Medical Birth Register, asthma severity and asthma control the year before pregnancy. We estimated both the crude ORs and adjusted for maternal age, BMI, parity, smoking at start of pregnancy, cohabitation/marital status, education and country of birth. To account for the clustering of observations within women with multiple deliveries the sandwich estimator for the standard errors was used. The Holm-Bonferroni method was used to evaluate what significant results from the primary analyses (i.e. adjusted analyses of maternal asthma yes/no and each of the outcome variables) there would be if applying an overall 5% significance level for those tests, To test for effect modification of asthma control by disease severity we included interaction terms in the models and tested for significance with likelihood-ratio test. STATA 12.1 was used for the analyses.

Permission for this study was obtained from the Regional Ethical Review board, "Regionala etikprövningsnämnden – EPN", in Stockholm, Sweden. In accordance with their decision, we did not obtain informed consent from participants involved in the study. All data were made anonymous prior to analyses.

Results

In this register-based cohort study, 284 214 pregnancies were completed in 266 045 women during the study period. The majority of women gave birth to only one child, but some women had two (18 003 women) or three (83 women) pregnancies within the period. Asthma was recorded for 26 586 (9.4%) of all pregnancies.

Maternal characteristics in relation to maternal asthma in any of the three registers are shown in Table 1. Compared to women without asthma, those with asthma were slightly younger (16.0% versus 14.6% below 25 years of age), had higher BMI, and were more often primiparous and smokers, more often born in Sweden, less often living with the baby's father and had lower education.

Maternal asthma was associated with an increased risk of almost all pregnancy complications, Table 2. For example, there was a 15% increased odds of preeclampsia or eclampsia (95% CI 1.06–1.24) in the group with maternal asthma and an 34% increased odds of haemorrhage during pregnancy (95% CI 1.12–1.60) and premature contractions which were increased by 52% (95% CI 1.29–1.80). There were also increased odds for adverse birth outcomes, including low birth weight and low gestational age. After adjusting for multiple testing most statistically significant associations remained except for lowest birth weight category and LGA. Subanalyses using asthma medication or diagnosis in the three different registers separately showed similar estimates, data not tabulated.

Among women with asthma in any of the health registers, 31% also had asthma medication recorded in the Medical Birth Register during pregnancy and only 0.4% had asthma medication during pregnancy if no asthma was noted in the registers, Figure 1a. According to the severity index, 13 034 (4.6% of the population) had asthma the year prior to conception. Of those, 32% were classified as mild controlled asthma, 37% as mild uncontrolled, 12% as moderate controlled, 15% as moderate uncontrolled, 0.6% as severe controlled and 4% as severe uncontrolled asthma. Among the 8962 women with mild asthma according to the severity index, 31% had asthma medication noted in the Medical Birth Register and 65% of the 4072 women with moderate or severe asthma, Figure 1b.

In the Medical Birth Register, treatment with asthma drugs was most commonly already present at the start of pregnancy or initiated during the first trimester, Figure 2. Most women continued their medication throughout the whole pregnancy or ended medication during the third trimester. Short-acting β2-agonists (SABA) and inhaled corticosteroids (ICS) medication were slightly more often discontinued during pregnancy compared to other asthma medications (LABA and LTRA). We were not able to assess whether this group of women were at higher risk of pregnancy complications than those who did not discontinue. There was however an increased risk of adverse pregnancy outcomes in women with asthma medication noted in the Medical Birth Register, similar to the main results.

For analyses on the association between asthma severity (moderate/severe asthma with mild asthma as reference) and adverse outcomes, no increased risks for the described pregnancy outcomes were seen, Table 3. For the association between labour characteristics and birth outcomes there were significant findings for vaginal instrumental delivery, emergency CS, and the children born to women with moderate/severe asthma were significantly smaller compared to those born to women with mild asthma.

In analyses of asthma control (uncontrolled versus controlled), for most outcomes we couldn't detect significant differences. However, pregnant women with uncontrolled asthma were at increased risk of instrumental vaginal delivery (OR 1.17 95% CI 1.03–1.34) compared to women with controlled asthma. An uncontrolled asthma also seemed to decrease the risk of premature contractions (OR 0.63, 95% CI 0.42–0.95) and low Apgar (OR 0.72 95% CI 0.52–0.99). There was significant effect modification (interaction) between asthma control and severity for premature rupture of the membranes ($p = 0.007$) and gestational age ($p = 0.011$). Uncontrolled asthma reduced the odds for premature rupture of the membranes for women with mild asthma (OR 0.65 95% CI 0.47–0.90), but not moderate/severe (OR 1.44 95% CI 0.88–2.35). For gestational age, there was a significantly increased risk of giving birth in week 37–38 if having uncontrolled asthma (OR 1.29 95% CI 1.07–1.56) among women with moderate/severe asthma but not among those with mild asthma, not shown in table.

Discussion

In this population-based cohort study of 284 214 pregnancies, we found that maternal asthma is a risk factor for a number of adverse pregnancy and labour outcomes such as preeclampsia/eclampsia and caesarean section, and perinatal outcomes such as SGA. We also showed an increased risk of some adverse outcomes with increasing asthma severity the year prior to pregnancy, including instrumental delivery, emergency caesarean section, birth weight 2000–3499 grams and SGA. The adverse impact of asthma in pregnancy on most outcomes is striking. Although increased risks of haemorrhage during pregnancy, premature contractions, placental abruption and SGA have been observed in some previous studies [5,6,9,12–14,28–30], the novelty with our results is the consistency in risk increases for women with asthma before and during pregnancy across all pregnancy and labour characteristics, as well as most perinatal outcomes. This has not

Table 1. Background characteristics of study population of 284 214 pregnancies by asthma status.

	Asthma* No	Asthma* Yes
	n = 257 628	n = 26 586
	n(%)	n(%)
Maternal Characteristics		
Age		
≤19	4312 (1.7)	519 (2.0)
20–24	33 316 (12.9)	3721 (14.0)
25–29	73 744 (28.6)	7626 (28.7)
30–34	89 948 (34.9)	8973 (33.8)
>34	56 308 (21.9)	5747 (21.6)
BMI		
<18,5	5763 (2.2)	518 (1.9)
18,5–24,9	145 226 (56.4)	13 288 (50.0)
25–29,9	57 913 (22.5)	6740 (25.4)
≥30	26 471 (10.3)	4222 (15.9)
Missing	22 255 (8.6)	1818 (6.8)
Parity		
1	149 334 (58.0)	16 065 (60.4)
2–3	94 090 (36.5)	8937 (33.6)
≥4	14 204 (5.5)	1584 (6.0)
Sex of offspring		
Girl	124 881 (48.5)	12 966 (48.8)
Boy	132 747 (51.5)	13 620 (51.2)
Cigarettes smoked/day		
0	229 737 (89.2)	23 452 (88.2)
1–9	12 774 (5.0)	1821 (6.8)
>9	3684 (1.4)	620 (2.3)
Missing	11 433 (4.4)	693 (2.6)
Country of birth		
Sweden	198 585 (77.1)	22 945 (86.3)
Denmark, Norway, Finland, Iceland	4051 (1.6)	411 (1.5)
Other countries	54 845 (21.3)	3221 (12.1)
Missing	147 (0.1)	9 (0.0)
Cohabitation/marital status		
Living with baby's father, married	105 247 (40.9)	9788 (36.8)
Living with baby's father, unmarried	124 405 (48.3)	14 107 (53.1)
Not living with baby's father	13 673 (5.3)	1840 (6.9)
Missing	14 303 (5.6)	851 (3.2)
Mother's education level		
≤9 years	27 491 (10.7)	3141 (11.8)
10–12 years	96 841 (37.6)	10 870 (40.9)
13–14 years	30 287 (11.8)	3124 (11.8)
≥15 years	92 756 (36.0)	9038 (34.0)
Missing	10 253 (4.0)	413 (1.6)

*Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register and/or asthma medication suspended at least twice according to the Swedish Prescribed Drug Register.

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been previously shown and has important public health implications.

We observed higher rate of caesarean section in asthma patients which is in agreement with most previous studies [9,10,13,31]. Higher rate of CS has also been observed in other chronic conditions [32–34] and it has been proposed that the higher rates of delivery interventions might be related to foetal stress associated with the underlying disease. However, we did not find an

Table 2. Associations between maternal asthma and pregnancy characteristics, labour characteristics and perinatal outcomes in a cohort of 284 214 pregnancies, reported as unadjusted and adjusted OR with 95% CI, all estimated by multinomial logistic regression.

	Number of pregnancies	Asthma§	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	P-values adjusted
	N (%)	n(%)			
Pregnancy Characteristics					
Preeclampsia or eclampsia	7797 (2.7)	915 (3.4)	1.30 (1.21–1.39)	1.15 (1.06–1.24)	<0.001*
Gestational diabetes	4804 (1.7)	534 (2.0)	1.22 (1.10–1.34)	1.09 (0.99–1.20)	0.066
Haemorrhage during pregnancy	1341 (0.5)	151 (0.6)	1.23 (1.03–1.48)	1.34 (1.12–1.60)	0.001*
Premature contractions	1497 (0.5)	211 (0.8)	1.59 (1.37–1.85)	1.52 (1.29–1.80)	<0.001*
Premature rupture of membranes	4630 (1.6)	544 (2.0)	1.30 (1.19–1.41)	1.30 (1.18–1.43)	<0.001*
Placental abruption	1053 (0.4)	136 (0.5)	1.44 (1.21–1.71)	1.44 (1.18–1.75)	<0.001*
Labour Characteristics					
Labour dystocia	29 523 (10.4)	3040 (11.4)	1.13 (1.08–1.17)	1.10 (1.06–1.15)	<0.001*
Mode of delivery					
Vaginal non-instrumental delivery	213 687 (75.2)	18 916 (71.2)	Ref.	Ref.	
Elective CS (before start of labour)	19 396 (6.8)	2191 (8.2)	1.31 (1.25–1.38)	1.29 (1.22–1.36)	<0.001*
Vaginal instrumental delivery	21 792 (7.7)	2105 (7.9)	1.10 (1.05–1.15)	1.11 (1.06–1.17)	<0.001*
Emergency CS prior to or after start of labour	27 632 (9.7)	3177 (11.9)	1.34 (1.29–1.39)	1.29 (1.23–1.34)	<0.001*
Missing	1707 (0.6)	197 (0.7)			
Haemorrhage after delivery	14 765 (5.2)	1413 (5.3)	1.03 (0.97–1.08)	1.03 (0.97–1.09)	0.358
Birth outcome and post-partum					
Birth weight, grams					
≤1999	3809 (1.3)	370 (1.4)	1.08 (0.96–1.20)	1.15 (1.02–1.29)	0.034
2000–2499	5811 (2.0)	637 (2.4)	1.23 (1.13–1.34)	1.32 (1.20–1.45)	<0.001*
2500–2999	30 118 (10.6)	3109 (11.7)	1.15 (1.10–1.20)	1.29 (1.23–1.34)	<0.001*
3000–3499	92 210 (32.4)	8615 (32.4)	1.03 (1.00–1.06)	1.12 (1.09–1.16)	<0.001*
≥3500	151 827 (53.4)	13 810 (51.9)	Ref.	Ref.	
Missing	439 (0.2)	45 (0.2)			
Gestational age, weeks					
≤31	2398 (0.8)	221 (0.8)	1.03 (0.89–1.18)	1.05 (0.90–1.22)	0.671
32–34	3489 (1.2)	371 (1.4)	1.20 (1.08–1.35)	1.19 (1.06–1.33)	0.002*
35–36	8757 (3.1)	1030 (3.9)	1.35 (1.26–1.44)	1.30 (1.21–1.39)	<0.001*
37–38	54 084 (19.0)	5601 (21.1)	1.17 (1.13–1.21)	1.18 (1.13–1.22)	<0.001*
39–40	145 298 (51.1)	13 061 (49.1)	Ref.	Ref.	
≥41	69 993 (24.6)	6293 (23.7)	1.00 (0.97–1.03)	0.97 (0.94–1.01)	0.165
Missing	195 (0.1)	9 (0.0)			
Small for gestational age					
Yes	6722 (2.4)	714 (2.7)	1.16 (1.07–1.25)	1.23 (1.13–1.33)	<0.001*
Missing	625 (0.2)	54 (0.2)			
Large for gestational age					
Yes	9639 (3.4)	977 (3.7)	1.10 (1.03–1.17)	0.93 (0.86–0.99)	0.035
Missing	625 (0.2)	54 (0.2)			
Apgar at 5 minutes <7	3322 (1.3)	384 (1.4)	1.10 (0.99–1.23)	1.08 (0.96–1.20)	0.198
Asphyxia or hypoxia	2873 (1.0)	297 (1.1)	1.12 (0.99–1.26)	1.07 (0.94–1.22)	0.291

In the unadjusted analyses n = 26 586 pregnancies were included in the asthma group. In the adjusted analyses n = 24 203 pregnancies were included in the asthma group.

§Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register and/or asthma medication suspended at least twice according to the Swedish Prescribed Drug Register.

†Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status and level of education.

*Significant after having adjusted for multiple hypotheses testing using the Holm-Bonferroni method.

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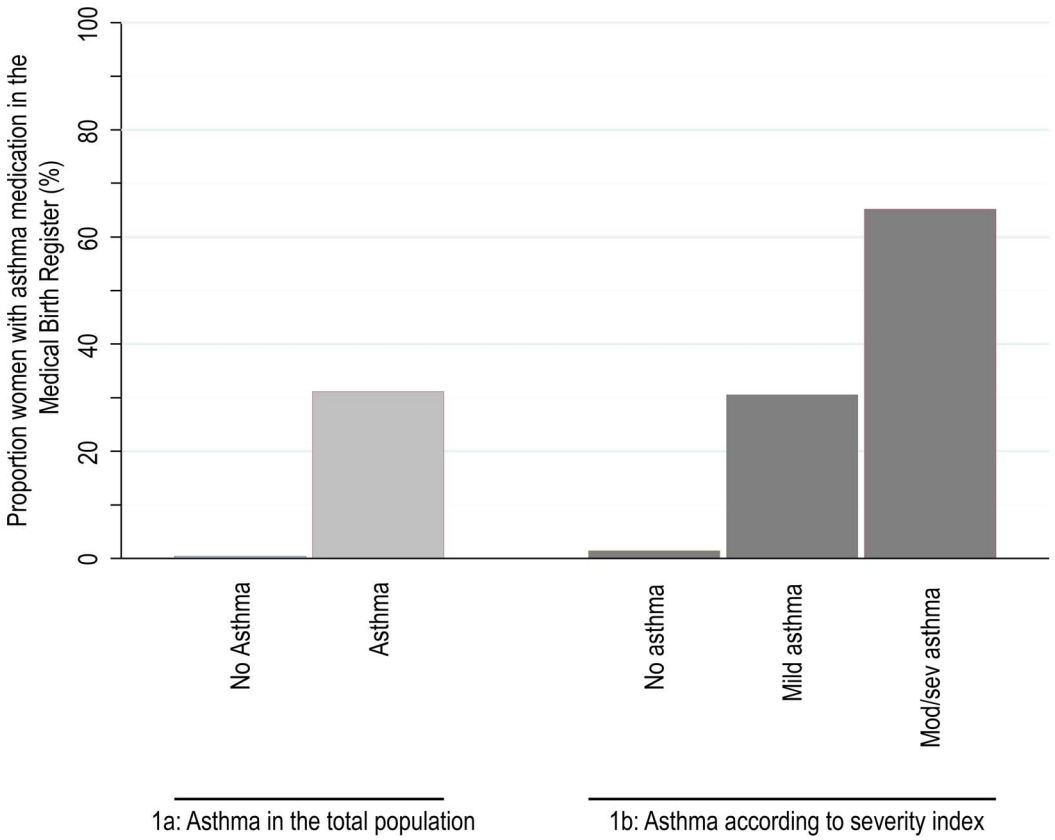

Figure 1. Asthma medication in the Medical Birth Register. a) Proportion of women with asthma medication recorded in the Medical Birth Register if asthma reported in the Medical Birth Register, National Patient Register or the Prescribed Drug Register. b) Proportion of women with asthma medication in the Medical Birth Register among those with no, mild and moderate/severe asthma according to the modified Firoozi severity index.
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association between asthma and low Apgar score or child hypoxia or asphyxia in the registers. It is possible that women with chronic disease in general are more likely to undergo surgery for a medical reason or because of health care professionals' assumption that vaginal delivery is associated with more complications [35].

We did not identify asthma as a risk factor for preterm delivery <32 weeks which is consistent with one previous study [8]. There was however an increased risk of late preterm birth (GA 32–36 weeks). In the past, much focus has been on infant mortality and morbidity in the very or extremely premature children but it is now clear that even moderate or late prematurity are risk factors for the child [36].

Some speculate that increased risks of preterm delivery among women with asthma may be due to similarities between bronchial and uterine smooth muscle hyperresponsiveness [30]. The association between maternal asthma in pregnancy and adverse outcomes may be caused by periods of intermittent hypoxia during pregnancy affecting oxygenation of placental and cord blood which in turn has a negative influence on the foetus. Such an interpretation is supported by the finding of a correlation between low FEV_1 during pregnancy and intrauterine growth retardation [37]. This hypothesis would also be supported if there were higher risk of pregnancy complications in women who discontinue their asthma medication during pregnancy. However we were not able to show this, perhaps due to the fact that in some women asthma improves during pregnancy [38]. There was an increased risk of adverse pregnancy outcomes such as placental abruption in women with asthma medication noted in the Medical Birth Register and hypoxia in the placenta could be a mechanism for abruption [39].

In separate analyses using asthma medication and diagnoses from the three separate registers, we observed increased risks of adverse outcomes similar to that of the overall analysis. This would suggest that asthma as such plays a key role in the adverse outcomes.

Women with uncontrolled asthma were at increased risk of instrumental vaginal delivery but also had decreased risk of premature contractions and low Apgar score and there was a slight interaction between asthma control and severity. These might be random findings or due to the overrepresented mild asthma group, but the lower risk of premature contractions might also be due to use of high doses of short acting beta agonists which are known to inhibit contractions of the uterus [40]. The findings should be further investigated in a clinical prospective cohort study on asthma severity, control and medication, where also discontinuation of medication can be further assessed.

The present study is the largest prospective to date with several strengths. Firstly, it is a population-based, longitudinal register based study in a unified health care environment with recording in medical registers of 280 000 singleton pregnancies in Sweden. In a cohort of the total population, we have the advantage that the results are representative and thus easily generalisable to the general population. Secondly, information on exposures and outcomes were prospectively collected, which precludes recall bias.

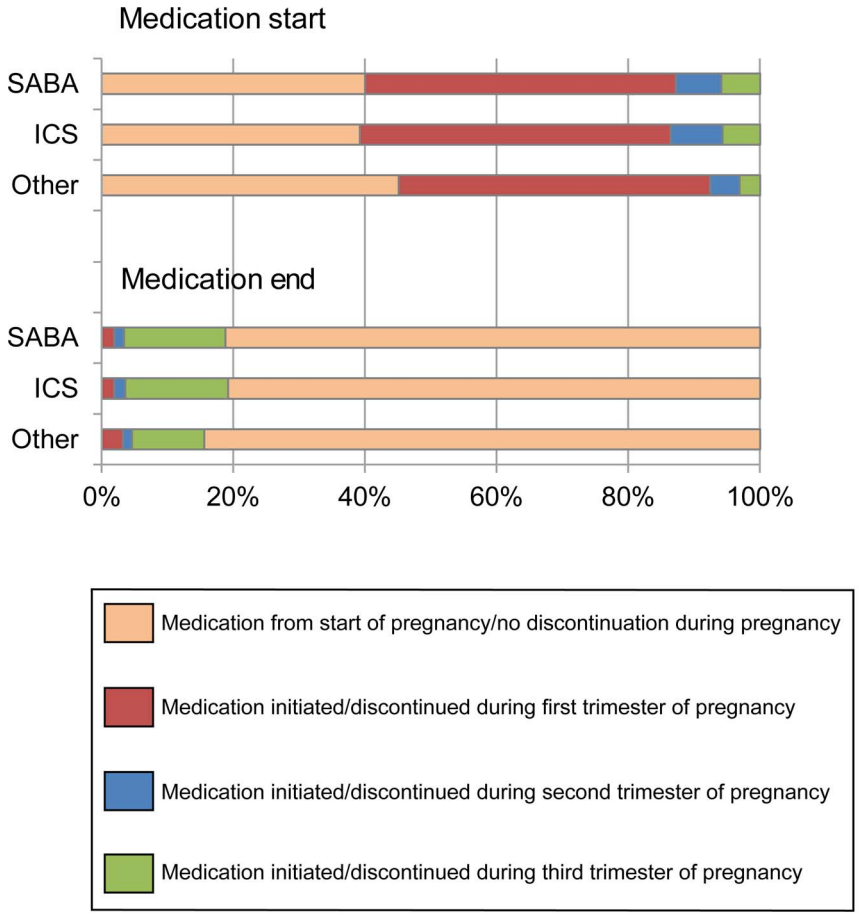

Figure 2. Asthma medication during trimesters. Starting and ending of treatment with asthma drugs (short-acting β2-agonists, SABA; inhaled corticosteroids, ICS and others (long-acting β2-agonists LABA and leukotriene receptor antagonist LTRA) in the Medical Birth Register.
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Thirdly, the asthma diagnosis was established by applying predetermined asthma criteria to the National Patient Register (covers inpatient and outpatient visits but not visits to general practitioners), the Prescribed Drug Register (full coverage of all dispensed asthma medication); and the Swedish Medical Birth Register (covers approximately 99% of the pregnancies >22 weeks [23,41]). In addition, the large sample gave us high statistical power.

There are also inherent limitations in register based studies. First, there may be residual confounding due to factors not recorded in the registers. We lack information on genetic factors, many pregnancy associated factors (e.g. maternal diet and passive smoking, physical activity or alcohol usage during pregnancy), and other factors related to both maternal asthma and pregnancy outcomes (e.g. health care utilisation patterns) [42]. Secondly, some posts in the Medical Birth Register are derived from automatic linking from other national registers whereas other variables such as asthma and medication rely on self-reporting to the midwife. Stephansson et al recently showed that the rate of reporting of medication in the Medical Birth Register is higher for more severe and chronic diseases. For asthma the agreement between the Prescribed Drug Register and the Medical Birth Register is around 58% [43]. We had however also access to maternal asthma diagnosis in the National Patient Register as well as medication in the Prescribed Drug Register, and detected higher estimates for the association between maternal asthma during pregnancy and outcomes in the National Patient Register and Prescribed Drug Register compared to the Medical Birth Register. Thirdly, asthma severity was assessed with an index developed in another country (Canada) and although Sweden and Canada are similar in many ways it's not certain the index validity is the same in Sweden. Our results indicate a need for increased awareness among midwives and obstetricians on the adverse effects of maternal asthma during pregnancy.

By increasing awareness of the population with maternal asthma before and during pregnancy and by doing so ensuring proper management, pregnancy and labour characteristics and perinatal outcomes would most likely improve. A study to test clinical guidelines for asthma in early pregnancy with a possibility of early asthma detection and asthma control intervention might be useful to women who are at risks of pregnancy complications, and a next step in further understanding the effects of the disease in pregnancy.

In conclusion, maternal asthma during pregnancy is associated with an increased risk of a number of serious pregnancy and labour complications and adverse perinatal outcomes. There is also an increased risk of a few adverse outcomes based on asthma severity and control. Greater awareness and improved asthma management would most likely improve outcomes.

Table 3. Associations between moderate/severe asthma according to the Firoozi index the year before pregnancy and perinatal outcomes in a cohort of 284 214 pregnancies, mild asthma as reference.

	Cases in mild asthma group	Cases in moderate-severe asthma group	Moderate/severe asthma vs Mild asthma	Moderate/severe asthma vs Mild asthma	P-values adjusted
	n (%)	n (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	
Pregnancy characteristics					
Preeclampsia or eclampsia	319 (3.6)	159 (3.9)	1.10 (0.89–1.35)	1.01 (0.81–1.26)	0.927
Gestational diabetes	188 (2.1)	85 (2.1)	0.99 (0.76–1.30)	0.97 (0.73–1.30)	0.850
Haemorrhage during pregnancy	54 (0.6)	27 (0.7)	1.10 (0.70–1.73)	1.13 (0.70–1.83)	0.612
Premature contractions	72 (0.8)	29 (0.7)	0.89 (0.56–1.41)	0.92 (0.59–1.43)	0.715
Premature rupture of membranes	167 (1.9)	88 (2.2)	1.16 (0.90–1.50)	1.20 (0.92–1.57)	0.182
Placental abruption	44 (0.5)	19 (0.5)	0.95 (0.53–1.71)	0.80 (0.46–1.40)	0.444
Labour characteristics					
Labour dystocia	1077 (12.0)	497 (12.2)	1.02 (0.91–1.14)	1.06 (0.94–1.19)	0.364
Mode of delivery					
Vaginal, non-instrumental delivery	6394 (71.3)	2767 (68.0)	Ref.	Ref.	
Elective CS (before start of labour)	732 (8.2)	358 (8.8)	1.13 (0.99–1.30)	0.99 (0.85–1.14)	0.861
Vaginal instrumental delivery	742 (8.3)	373 (9.2)	1.16 (1.01–1.34)	1.19 (1.03–1.37)	0.020
Emergency CS prior to or after onset of labour	1024 (11.4)	537 (13.2)	1.21 (1.08–1.36)	1.18 (1.04–1.33)	0.012
Missing	70 (0.8)	37 (0.9)			
Haemorrhage after delivery	499 (5.6)	222 (5.5)	0.98 (0.83–1.15)	1.03 (0.86–1.24)	0.728
Birth outcome and post-partum					
Birth weight, grams					
≤1999	123 (1.4)	56 (1.4)	1.07 (0.77–1.48)	0.99 (0.68–1.44)	0.964
2000–2499	184 (2.1)	113 (2.8)	1.44 (1.14–1.82)	1.45 (1.13–1.86)	0.004
2500–2999	966 (10.8)	539 (13.2)	1.31 (1.17–1.47)	1.39 (1.22–1.57)	<0.001
3000–3499	2907 (32.4)	1328 (32.6)	1.07 (0.99–1.16)	1.14 (1.04–1.25)	0.004
≥3500	4766 (53.2)	2031 (49.9)	Ref.	Ref.	
Missing	16 (0.2)	5 (0.1)			
Gestational age, weeks					
≤31	82 (0.9)	38 (0.9)	1.03 (0.69–1.54)	0.92 (0.59–1.42)	0.696
32–34	107 (1.2)	47 (1.2)	0.98 (0.68–1.40)	0.96 (0.66–1.39)	0.813
35–36	318 (3.5)	154 (3.8)	1.08 (0.88–1.32)	1.04 (0.84–1.28)	0.719
37–38	1802 (20.1)	863 (21.2)	1.07 (0.96–1.18)	1.05 (0.94–1.16)	0.399
39–40	4399 (49.1)	1978 (48.6)	Ref.	Ref.	
≥41	2254 (25.2)	992 (24.4)	0.98 (0.89–1.07)	0.99 (0.90–1.09)	0.824
Missing	0 (0.0)	0 (0.0)			
Small for gestational age					
Yes	204 (2.3)	153 (3.8)	1.68 (1.35–2.08)	1.71 (1.34–2.17)	<0.001
Missing	16 (0.2)	5 (0.1)			
Large for gestational age					
Yes	375 (4.2)	127 (3.1)	0.74 (0.60–0.91)	0.65 (0.52–0.81)	<0.001
Missing	16 (0.2)	5 (0.1)			
Apgar at 5 minutes <7	132 (1.5)	69 (1.7)	1.15 (0.86–1.54)	1.17 (0.86–1.59)	0.320
Asphyxia or hypoxia	110 (1.2)	53 (1.3)	1.06 (0.76–1.49)	1.12 (0.80–1.57)	0.495

Unadjusted and adjusted model (n = 249 006) estimated by multinomial logistic regression with OR and 95% CI. In unadjusted analyses n = 8962 were included in the mild asthma group and n = 4072 in the moderate/severe group. In the adjusted analyses n = 7996 were included in the mild and n = 3646 in the moderate/severe group. *Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status and level of education.

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Supporting Information

Appendix S1 Asthma severity according to Firoozi et al [21].
(DOCX)

Author Contributions

Conceived and designed the experiments: GR CL CA. Performed the experiments: GR. Analyzed the data: GR. Contributed to the writing of the manuscript: GR CL KL TG SS CA. Assisted in the statistical analyses: CL.

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