

ORIGINAL ARTICLE

The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis

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Abstract

Objective: To investigate if maternal asthma is associated with an increased risk of maternal and placental complications in pregnancy.

Methods: Electronic databases were searched for the following terms: (asthma or wheeze) and (pregnan* or perinat* or obstet*). Cohort studies published between January 1975 and March 2012 were considered for inclusion. Forty publications met the inclusion criteria, reporting at least one maternal or placental complication in pregnant women with and without asthma. Relative risk (RR) with 95% confidence intervals (CIs) was calculated.

Results: Maternal asthma was associated with a significantly increased risk of cesarean section (RR = 1.31, 95%CI = [1.22–1.39]), gestational diabetes (RR = 1.39, 95%CI = [1.17–1.66]), hemorrhage (antepartum: RR = 1.25, 95%CI = [1.10–1.42]; postpartum: RR = 1.29, 95%CI = [1.18–1.41]), placenta previa (RR = 1.23, 95%CI = [1.07–1.40]), placental abruption (RR = 1.29, 95%CI = [1.14–1.47]) and premature rupture of membranes (RR = 1.21, 95%CI = 1.07–1.37). Moderate to severe asthma significantly increased the risk of cesarean section (RR = 1.19, 95%CI = [1.09–1.31]) and gestational diabetes (RR = 1.19, 95%CI = [1.06–1.33]) compared to mild asthma. Bronchodilator use was associated with a significantly lowered risk of gestational diabetes (RR = 0.64, 95%CI = [0.57–0.72]).

Conclusions: Pregnant women with asthma are at increased risk of maternal and placental complications, and women with moderate/severe asthma may be at particular risk. Further studies are required to elucidate whether adequate control of asthma during pregnancy reduces these risks.

Keywords

Asthma, maternal and placental complications, meta-analysis, pregnancy

History

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Introduction

Asthma is a common medical condition to complicate pregnancy, with between 3 and 12% of women affected [1–3]. The course of the disease can change during pregnancy, and there are reports of adverse perinatal outcomes associated with maternal asthma. In our previous systematic review and meta-analyses, we found maternal asthma to be associated with a moderate but significantly increased risk of low birth weight, preterm birth and pre-eclampsia [4]. There have been many studies reporting other adverse perinatal outcomes related to the mother and placenta [5]. There are several

reasons why these complications may be heightened by asthma. Asthmatics have altered placental function [6], but it is unclear whether this also manifests as an increase in placental complications during pregnancy. Asthma exacerbations are an important complication during pregnancy that might prompt early delivery by cesarean section. The obesity epidemic is associated with both gestational diabetes, but also worsening asthma in the context of pregnancy, and so there may be associations between these key risk factors during pregnancy. While one might expect increased placental and maternal complications from asthma in pregnancy, the published data to support this are not consistent and vary considerably in terms of sample size, study design and control for potential confounders such as ethnicity, smoking, socio-economic status and asthma treatment and control. In the current systematic review and meta-analysis, we sought to investigate whether maternal asthma is associated with an

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increased risk of maternal and placental complications, including caesarean delivery, gestational diabetes and hemorrhage. We also explored whether asthma severity or management influenced the risks.

Methods

Search strategy and selection criteria

The electronic databases PubMed, Embase, the Cochrane Clinical Trials Register and CINAHL were searched for cohort studies published between 1975 and March 2012, using the search terms (asthma or wheeze) and (pregnan* or perinat* or obstet*). All identified abstracts were independently assessed by two reviewers. The full-text version of each potential article was obtained for assessment by two reviewers to establish whether it met the inclusion criteria.

Maternal asthma was defined as physician diagnosed (confirmed or subject self-report), database-coded asthma diagnosis or asthma fulfilling American Thoracic Society criteria. Included articles were prospective or retrospective cohorts and contained data from a group of pregnant women with and without asthma (analysis A) or a group of pregnant women with asthma which had been stratified according to medication use (inhaled corticosteroid [ICS] use or no ICS use, bronchodilator use or no bronchodilator use, oral steroid use or no oral steroid use), asthma severity (mild or moderate/severe) or asthma exacerbations during pregnancy (analysis B). Further inclusion criteria were reporting at least one maternal (cesarean delivery and gestational diabetes) or placental (antepartum and postpartum hemorrhage, placenta previa, placental abruption, chorioamnionitis, or premature rupture of membranes; PROM) outcome of interest in women with and without asthma (analysis A), or sub-groups of women with asthma (analysis B).

For sub-group analyses of asthmatic women by exacerbation or asthma severity, there were variations in the definitions used for exacerbation, mild and moderate/severe asthma in the primary studies which are outlined in Table S2.

Data extraction and quality assessment

Data extraction was undertaken using a standardized form by one reviewer and checked by a second reviewer. Disagreements were resolved by consensus between investigators. The following details were extracted: study design, study characteristics (year and country of study), subject characteristics (gestational age at recruitment, subject exclusions, maternal age, body mass index (BMI), smoking, socio-economic status, prenatal care, race/ethnicity and co-morbidities), asthma diagnosis, severity, management and perinatal outcome data for asthma and control groups (reported as n [%], mean [SD] or adjusted odds ratios). Active asthma management was defined as the involvement of the study investigators in the management of subjects with asthma, which had been explicitly outlined in the methods of the primary paper. The quality of each study was assessed independently and scored by two reviewers using the Newcastle–Ottawa scale (NOS) [7]. The NOS is a validated tool for assessing the quality of non-randomized studies, including cohort studies, and has a maximum score of 9.

Statistical analysis

Our meta-analyses conformed to standard methodological guidelines for meta-analysis of observational studies [8]. For dichotomous outcomes, the relative risk (RR) with 95% confidence interval (CI) was calculated using a random effects model. The difference between RRs for the active management and no active management subgroups was determined using Altman and Bland's method [9], and expressed as a relative risk ratio (RRR) with 95%CI. Where original data had been adjusted for potential confounding factors, adjusted odds ratios were pooled using the generic inverse variance method. Heterogeneity was examined using the chi-square test (with $p < 0.1$ indicating significant heterogeneity), the I^2 parameter and meta-regression when appropriate (at least 10 studies). Funnel plots and the Egger test were used to investigate study size effects indicating possible publication bias when outcomes were reported in at least 10 studies. Power calculations were conducted using the power and sample size program PS 2.1.30 [10]. The majority of the analyses were performed using Review Manager software (Review Manager (RevMan)) [Computer program] Version 4.3.2 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, available online <http://ims.cochrane.org/revman/download/revman-4>. Meta-regression and publication bias detection were performed using Stata9.0 (Stata Corporation, www.stata.com). Potential explanatory variables such as event rate, study design (retrospective/prospective), continent of study, decade conducted and participant characteristics (proportion experiencing an exacerbation, proportion using ICS, difference between asthma and control groups for current smokers and maternal age) were included in the meta-regression.

Results

Included studies, study characteristics and quality of reporting

Our search strategy initially yielded a total of 5292 studies from Medline ($n = 2323$), Embase (2379), CINAHL ($n = 501$) and the Cochrane Clinical Trials Register ($n = 89$). A total of 138 papers were identified for possible inclusion in the review. Of these, 98 publications were excluded for the following reasons: no control group ($n = 32$), no clear asthma group ($n = 6$), asthma subgroups that did not meet our inclusion criteria ($n = 16$), asthma subjects selected by exacerbation only ($n = 3$), study published after 1975 but conducted prior to 1975 ($n = 2$), cross-sectional survey ($n = 3$), abstract only ($n = 5$), asthma subgroups only compared with control group ($n = 8$), no perinatal outcomes reported ($n = 10$), review article ($n = 6$), paper retracted ($n = 1$) and case-control study design ($n = 8$). Forty papers describing 15 prospective and 21 retrospective cohort studies met the criteria for analysis A ($n = 26$), analysis B ($n = 9$) or both ($n = 5$) and are included in this article because they described relevant maternal and placental outcomes [3,11–49] (Table S1). Quality scores of the papers ranged from 4 to 9 (mean 7.8; SD 1.2). All were considered to be of acceptable quality for inclusion.

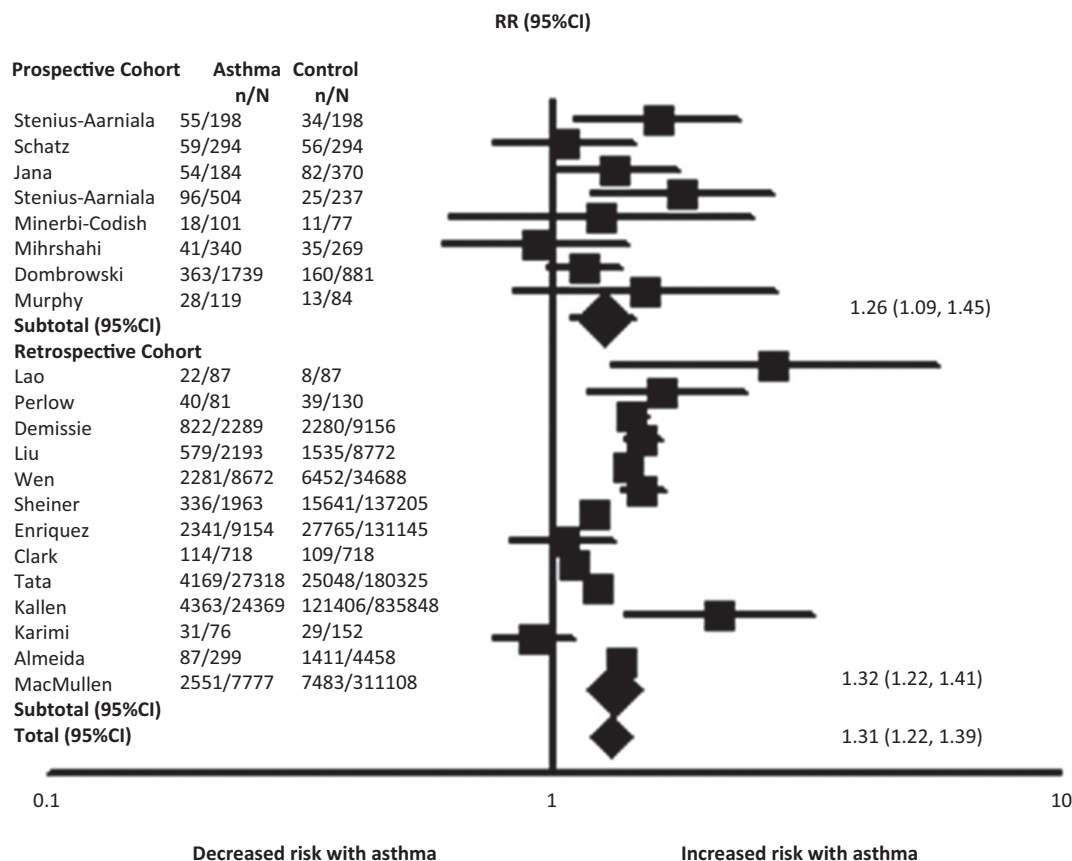


Figure 1. Meta-analysis of prospective and retrospective cohort studies for caesarean delivery in pregnant women with and without asthma. RR, relative risk and CI, confidence interval.

Cesarean delivery

Women with asthma had a significantly greater risk of cesarean section delivery than women without asthma (RR = 1.31, 95%CI = [1.22–1.39], Figure 1, Table 1), although there was significant heterogeneity between studies ($I^2 = 90.8\%$, $p < 0.001$). There were six studies where subjects' asthma had been actively managed [11–16] and 15 studies without active asthma management included in the meta-analysis [1,17–30]. In both sub-categories, there was an increased risk of cesarean delivery in women with asthma, compared to women without asthma (Table 2) and no difference between the management sub-groups (RRR = 1.00, 95%CI = [0.84–1.18], $p = 0.19$).

In a univariate meta-regression, heterogeneity could be partially explained by the proportion of subjects experiencing an exacerbation during the study ($p = 0.027$) and by the age difference between asthma and control groups ($p = 0.012$, Table 3). Multiple meta-regression added no further information to the variance between studies ($p > 0.05$). Publication bias was not significant (Egger's test, $p = 0.148$).

Four studies reported adjusted odds ratio data for cesarean delivery [21–23,26] and were combined in a separate meta-analysis. Women with asthma were at increased odds of cesarean delivery compared to women without asthma (OR = 1.43, 95%CI = [1.16–1.75]), with significant heterogeneity between studies ($I^2 = 97.1\%$, $p < 0.001$).

Some studies presented data for elective and emergency cesarean deliveries separately. Reasons for elective or emergency deliveries were not provided in the primary

publications. There was a significantly increased risk for elective cesarean delivery among women with asthma (RR = 2.14, 95%CI = [1.16–3.95]) but no increased risk for emergency cesarean delivery among women with asthma (RR = 1.03, 95%CI = [0.84–1.26]) (Table 1).

Subjects with moderate to severe asthma were at increased risk for cesarean section compared to those with mild asthma (RR = 1.19, 95%CI = [1.09–1.31], $n = 3$ studies [15,17,31]; Table 2). There was no increased risk for emergency cesarean delivery in women with moderate/severe asthma or asthma exacerbations in pregnancy compared to those with mild asthma or without exacerbations in pregnancy (Table 2). In addition, there was no evidence of an increased risk of cesarean section for women with asthma who used bronchodilators or ICS compared to women with asthma not using these medications (Table 2).

Gestational diabetes

There was a significantly increased risk of gestational diabetes among women with asthma compared to women without asthma (RR = 1.39, 95%CI = [1.17–1.66], Table 1, heterogeneity, $I^2 = 88.4\%$, $p < 0.001$). The risk was significant in the retrospective cohort sub-category only (RR = 1.45, 95%CI = [1.18–1.78], heterogeneity not significant, $I^2 = 0\%$) and confirmed after adjustment for covariates in four studies [23,26,30,32], (OR = 1.66, 95%CI = [1.53–1.79]). There was no significant publication bias (Egger test, $p = 0.922$).

When analyzed according to asthma management sub-categories, there was a significantly increased risk of

Table 1. Pooled results of maternal and placental complications in pregnant women with and without asthma.

Complications	Number of studies	Asthma group	Non-asthma group	Relative risk (95%CI)	Heterogeneity (I^2)
Cesarean section	21	18 450/88 475	209 622/1376 202	1.31 [1.22–1.39]	90.8%
Prospective	8	714/3479	416/2410	1.26 [1.09–1.46]	24.6%
Retrospective	13	17736/84 996	209 206/1373 792	1.32 [1.22–1.39]	94.2%
Emergency cesarean section	5	215/3246	155/2121	1.03 [0.84–1.26]	0.0%
Prospective	3	135/2441	77/1316	1.04 [0.79–1.36]	0.0%
Retrospective	2	80/805	78/805	1.19 [0.62–2.31]	60.4%
Elective cesarean section	5	156/1689	77/1604	2.14 [1.16–3.95]	69.4%
Prospective	3	100/884	38/799	2.41 [1.10–5.28]	71.3%
Retrospective	2	56/805	39/805	2.92 [0.28–31.03]	66.7%
Gestational diabetes	19	2956/99 700	16 437/1304 675	1.39 [1.17–1.66]	88.4%
Prospective	9	173/4239	89/2862	1.16 [0.90–1.50]	0.0%
Retrospective	10	2783/95 461	16 348/13 01 813	1.45 [1.18–1.78]	93.9%
Antepartum hemorrhage	11	1389/86 365	14 057/1382 224	1.25 [1.10–1.42]	71.3%
Prospective	2	13/686	23/601	0.61 [0.12–2.13]	74.2%
Retrospective	9	376/85 679	14 057/1382 224	1.29 [1.17–1.43]	60.0%
Postpartum hemorrhage	10	1436/61 552	6161/533 662	1.29 [1.18–1.41]	39.1%
Prospective	2	135/2099	58/1176	1.09 [0.56–2.12]	63.9%
Retrospective	8	1301/59 453	6103/532 486	1.30 [1.18–1.42]	41.3%
Placenta previa	8	250/76 525	3470/1251 079	1.23 [1.07–1.40]	0.0%
Prospective	NA	NA	NA	NA	NA
Retrospective	8	250/76 525	3470/1251 079	1.23 [1.07–1.40]	0.0%
Placental abruption	11	966/90 327	6649/1279 121	1.29 [1.14–1.47]	44.8%
Prospective	2	7/702	3/435	1.43 [0.37–5.52]	0.0%
Retrospective	9	959/89 625	8646/1279 121	1.29 [1.13–1.48]	54.1%
Chorioamnionitis	7	1425/37 714	2855/126 624	1.45 [0.96–2.22]	97.1%
Prospective	1	103/1739	44/881	1.19 [0.84–1.67]	NA
Retrospective	6	1322/35 975	2811/125 743	1.50 [0.94–2.40]	97.6%
Premature rupture of membrane	9	1897/48 147	24817/1057 576	1.21 [1.07–1.37]	74.6%
Prospective	3	34/884	42/799	0.91 [0.52–1.58]	20.0%
Retrospective	6	1863/47 263	24775/1056 777	1.23 [1.09–1.39]	81.5%

Table 2. Effects of active management, asthma severity/exacerbation, bronchodilator and inhaled corticosteroids on maternal and placental complications in pregnant women with and without asthma.

Items	Complications	Number of studies	Asthma group	Control group	Relative risk (95%CI)	Heterogeneity (I^2)
Active management	Cesarean section	6	655/3038	370/2064	1.31 [1.11–1.53]	32.4%
	Postpartum hemorrhage	3	138/2186	59/1263	1.18 [0.67–2.07]	39.9%
	Gestational diabetes	7	126/3245	69/2290	1.08 [0.81–1.46]	0.0%
No active management	Cesarean section	15	17 855/85 437	209 252/1374 138	1.31 [1.22–1.42]	94.0%
	Postpartum hemorrhage	6	1298/59 366	6102/532 399	1.29 [1.18–1.42]	47.4%
	Gestational diabetes	12	2830/96 455	16 368/1302 385	1.45 [1.20–1.76]	92.6%
Bronchodilator use	Cesarean section	3	Asthma group with characteristic 100/466	Asthma group without characteristic 123/696	1.14 [0.90–1.45]	0.0%
	Postpartum hemorrhage	2	28/255	37/268	0.86 [0.54–1.36]	0.0%
	Gestational diabetes	2	444/7340	576/6116	0.64 [0.57–0.72]	16.8%
ICS use	Cesarean section	4	530/3641	1165/8396	1.05 [0.96–1.16]	44.1%
	Cesarean section	3	538/2339	1503/7727	1.19 [1.09–1.31]	0.0%
Asthma severity (moderate to severe)	Emergency cesarean section	2	203/2287	764/7678	1.09 [0.94–1.27]	0.0%
	Gestational diabetes	3	384/4557	1392/18 415	1.19 [1.06–1.33]	65.5%
Asthma exacerbation	Emergency cesarean section	2	6/99	43/549	0.65 [0.27–1.56]	0.0%
	Gestational diabetes	2	7/72	22/512	2.02 [0.82–4.95]	0.0%

gestational diabetes in studies with no active asthma management only (RR = 1.45, 95%CI = [1.20–1.76]) (Figure 2; Table 2). There was no increased risk of gestational diabetes among studies where active asthma management had been provided (RR = 1.08, 95%CI = [0.81–1.46]). The difference between the no active management and active

management sub-categories was not quite significant (RRR = 0.74, 95% CI = [0.52–1.06], $p = 0.099$).

There was an increased risk for gestational diabetes among women with moderate to severe asthma, compared to women with mild asthma (RR = 1.19, 95%CI = [1.06–1.33], $n = 3$ studies [15,31,33]) and a significantly decreased risk for

Table 3. Weighted meta-regression analyses for potential sources of heterogeneity in cesarean delivery and gestational diabetes.

Complications	Covariate	No. of studies	Exp coefficient (SE)	p value
Cesarean delivery	Control event rate	21	0.55 (0.45)	0.468
	Retrospective versus prospective design	21	1.04 (0.11)	0.702
	Active versus non active management	21	1.06 (0.12)	0.608
	Country versus USA:	20		
	Europe		0.80 (0.08)	0.044
	Asia/Middle East		1.20 (0.13)	0.116
	Scandinavia		1.0 (0.10)	0.986
	Australia		0.82 (0.17)	0.354
	South America		0.68 (0.10)	0.023
	Decade versus 1980s	18		
	1990s		0.88 (0.09)	0.253
	2000s		0.85 (0.10)	0.181
	2010s		0.79 (0.11)	0.109
	Proportion with exacerbation	7	1.0 (0.001)	0.027
	Proportion using ICS	10	1.0 (0.003)	0.383
	Smokers (asthma-control)	10	0.99 (0.02)	0.495
	Age (asthma-control)	9	1.13 (0.04)	0.010
Gestational diabetes	Control event rate	19	0.01(0.07)	0.394
	Retrospective versus prospective design	19	1.20(0.25)	0.389
	Active versus no active management	19	0.77 (0.18)	0.286
	Country versus USA:	18		
	Europe		0.59 (0.16)	0.068
	Asia/Middle East		1.47(1.32)	0.677
	Scandinavia		0.73 (0.18)	0.232
	Australia		0.67 (0.19)	0.169
	Decade versus 1980s	17		
	1990s		1.27 (0.38)	0.432
	2000s		10.95 (0.32)	0.887
	2010s		1.38 (0.55)	0.439
	Proportion with exacerbation	8	1.01 (0.01)	0.078
	Proportion using ICS	8	1.00 (0.005)	0.882
	Smokers (asthma- control)	9	1.03 (0.04)	0.496
	Age (asthma-control)	11	1.14 (0.14)	0.333

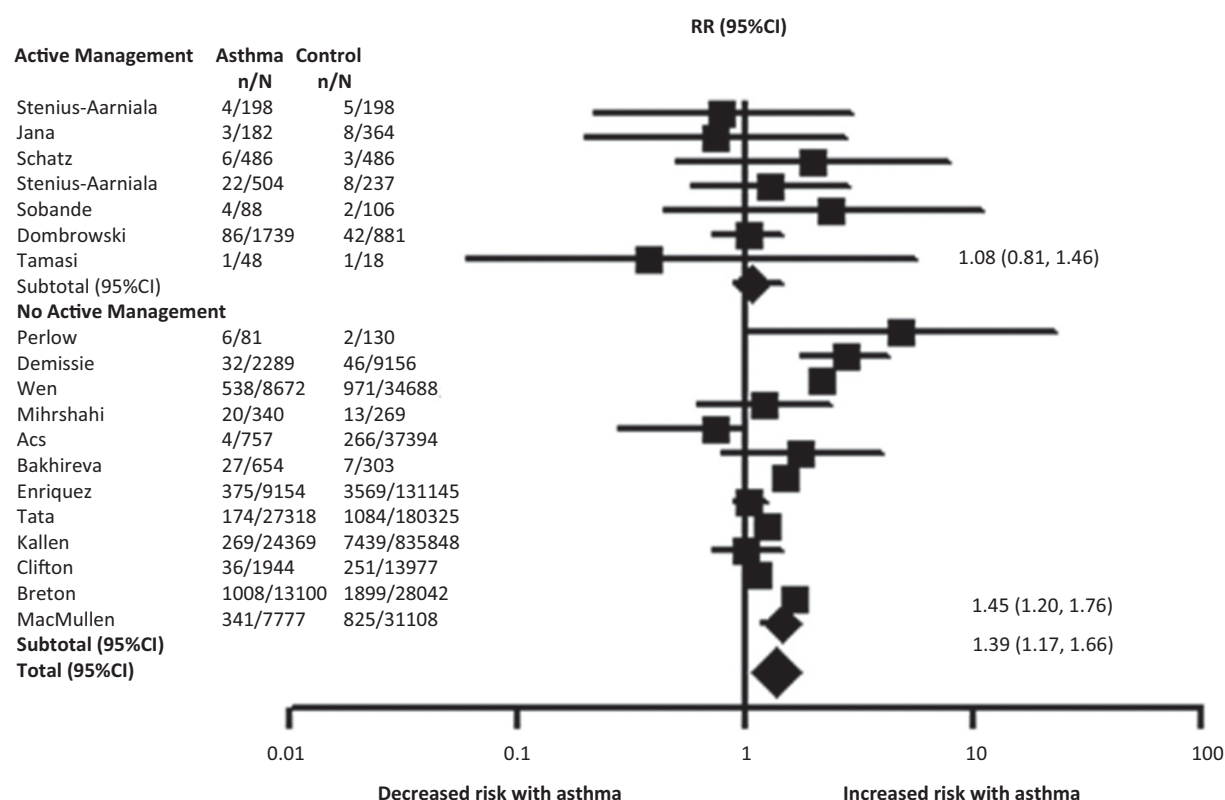


Figure 2. Meta-analysis of cohort studies for gestational diabetes by active management in pregnant women with asthma. RR, relative risk and CI, confidence interval.

gestational diabetes among users of bronchodilators compared to non-users ($RR = 0.64$, $95\%CI = [0.57-0.72]$, $n = 2$ studies [34,35]) (Table 2). There was an increased RR for gestational diabetes among women with asthma exacerbations compared to women without asthma exacerbations during pregnancy; however, this was not significant ($RR = 2.02$, $95\%CI = [0.82-4.95]$, $n = 2$ studies [37,46]).

Hemorrhage

There was a significantly increased risk of antepartum hemorrhage among women with asthma ($RR = 1.25$, $95\%CI = [1.10-1.42]$) compared to women without asthma, with significant heterogeneity between studies ($I^2 = 71.3\%$, $p < 0.001$; Table 1).

There was a significantly increased risk of postpartum hemorrhage among women with asthma compared to women without asthma ($RR = 1.29$, $95\%CI = [1.18-1.41]$, low heterogeneity $I^2 = 39.1\%$, $p = 0.1$). The risk of postpartum hemorrhage was significant in the retrospective cohort sub-category only ($RR = 1.30$, $95\%CI = [1.18-1.42]$). The prospective cohort studies [15,38] were underpowered (40%) to detect a RR of 1.30, as observed in the retrospective studies.

There were three cohort studies where subjects received active asthma management [15,19,38] and seven cohort studies where no active management was given [21-26, 30]. The risk of postpartum hemorrhage in women with asthma was significant in the no active management sub-category only ($RR = 1.29$, $95\%CI = [1.18-1.42]$) and confirmed by adjustment for covariates in four studies [21-23,26] ($OR = 1.30$, $95\%CI = [1.11-1.52]$, moderate heterogeneity [$I^2 = 68.6\%$, $p = 0.02$]). The active management studies were underpowered (38.5%) to detect a RR of 1.29, as observed in the no active management studies ($RR = 1.18$, $95\%CI = [0.67-2.07]$), and the difference between the RR s was not significant ($RRR = 0.91$, $95\%CI = [0.52-1.62]$) (Table 2).

There was no increased risk of postpartum hemorrhage in women who used bronchodilators compared to women who did not use bronchodilators ($RR = 0.86$, $95\%CI = [0.54-1.36]$) (Table 2).

Placenta previa

Women with asthma had a significantly increased risk of placenta previa compared to women without asthma ($RR = 1.23$, $95\%CI = [1.07-1.40]$, Table 1). This increased risk remained significant after adjustment for covariates in five studies ($OR = 1.39$, $95\%CI = [1.17-1.67]$).

Placental abruption

There was a significantly increased risk of placental abruption among women with asthma compared to women without asthma ($RR = 1.29$, $95\%CI = [1.14-1.47]$, with moderate heterogeneity, $I^2 = 44.8\%$, $p = 0.05$, Table 1), which was confirmed after adjustment for covariates in five retrospective studies with no active management ($OR = 1.46$, $95\%CI = [1.23-1.72]$, low heterogeneity, $I^2 = 27.7\%$, $p = 0.24$). The risk was significant in the retrospective cohort sub-category only ($RR = 1.29$, $95\%CI = [1.13-1.48]$),

which had a much larger sample size than the prospective cohort sub-category (Table 1).

Chorioamnionitis

Data on chorioamnionitis were included in three publications (one prospective cohort [15] and two retrospective cohort studies [22,39]) and infection of the amniotic cavity in four publications (all retrospective cohorts [21,23,30,41]). These two terms were considered synonymous. There was no increased risk of chorioamnionitis with maternal asthma in data from six retrospective cohort studies ($RR = 1.50$, $95\%CI = [0.94-2.40]$) or overall ($RR = 1.45$, $95\%CI = [0.95-2.22]$, Table 1). However, the four studies that reported adjusted odds ratio data showed a significantly increased odds of chorioamnionitis among women with asthma ($OR = 2.17$, $95\%CI = [1.97-2.39]$).

Premature rupture of membranes

There was a significantly increased risk of PROM among women with asthma ($RR = 1.21$, $95\%CI = [1.07-1.37]$) compared to women without asthma (Table 1). The risk was significant in the retrospective cohort sub-category only ($RR = 1.23$, $95\%CI = [1.09-1.39]$). The prospective cohort studies had 18% power to detect a RR of 1.23. Women with asthma had an increased odds of PROM compared to women without asthma in four studies (retrospective, no active management) reporting adjusted odds ratios [21-23,30] ($OR = 1.34$, $95\%CI = [1.26-1.44]$).

Discussion

Our meta-analyses found that maternal asthma was associated with increased risks of caesarean delivery, gestational diabetes and placental complications. Pregnant women with asthma have a 31% increased risk for caesarean delivery and twice the risk of elective C section. The number of studies that investigated caesarean delivery was large, and the risk in the presence of maternal asthma was increased in all sub-categories of study design and active management and in four studies that provided adjusted odds ratio data, with no apparent trends over time. This increased risk was not related to an increase in emergency cesareans (for either fetal or maternal indications) but rather a more than doubling in risk for elective caesarean delivery. Although generally C section is more likely to be indicated for obstetric reasons than asthma, asthma is associated with a number of conditions that may contribute to C section, such as maternal obesity, placental complications and intrauterine fetal growth restriction (IUGR). If women have severe asthma exacerbations, which are thought to be affecting the fetus (perhaps IUGR is detected), or if the pregnancy itself is affecting the asthma, then an elective C section may be the result. However, explanations on why asthma was associated with a significant risk for elective caesarean delivery but not emergent caesarean delivery is needed to be further studied.

In the Swedish Medical Birth Registry study, the risk of caesarean delivery remained after excluding women with medical conditions known to be associated with caesarean deliveries, such as gestational diabetes and pre-eclampsia [27]. ICS exposure has potential bidirectional roles for

pregnancies of women with asthma. On the one hand, it could improve poor asthma control, which affects placental function and fetal growth. On the other hand, it could inhibit maternal hormone concentrations. Therefore, although we found asthma severity related to a higher risk of cesarean delivery, our results from the available literature did not have sufficient power to demonstrate that active management and therapy, including ICS and bronchodilators for pregnant women with asthma, could decrease those risks. An additional explanation for not seeing a reduction in risks in women with asthma receiving medications could be confounding by severity.

Meta-regression was used to investigate the significant heterogeneity between studies reporting cesarean delivery as an outcome. This analysis indicated that differences in maternal age and exacerbations may contribute to some heterogeneity in the subset of studies that reported these covariates. It is clinically appropriate that older age or severe asthma exacerbations may increase the need for cesarean delivery. However, despite the significant heterogeneity, the results of the majority of studies were consistent in demonstrating an adverse risk associated with maternal asthma. Heterogeneity was also likely to be influenced by the large sample sizes of most studies (particularly the retrospective studies) where the variance was very small. This is the most likely explanation for the observed heterogeneity. Maternal asthma increased the risk of gestational diabetes by 40%. This is a particularly robust result, in that the risk was demonstrated in both retrospective and prospective studies, found in studies that adjust for confounding factors, showed no publication bias, and was diminished by active treatment. However, only one study controlled for the potential confounder of maternal BMI [26], which could confound the effect since obesity may be more likely in women with asthma and may contribute to the incidence of asthma exacerbations in pregnancy. In studies where active asthma management was conducted, there was a reduction in the RR of gestational diabetes (from 1.45 to 1.08). One possible mechanism for this would be prevention of exacerbations requiring oral corticosteroids, which may increase the risk of gestational diabetes [20].

The placenta is a vital organ for human fetal growth and survival. Alterations in placental vascular function [6], placental cortisol metabolism [16,50,51] and placental morphology [52] have been associated with maternal asthma and may contribute to reduced fetal growth in these pregnancies. For example, in asthmatic placentas, there was significant reduction in activity of the cortisol metabolizing enzyme 11 β -hydroxysteroid dehydrogenase type 2, which was associated with reduced fetal growth among mothers who did not use ICS treatment during pregnancy [51,52]. In this review, we analyzed the risks of major placental complications such as placenta previa, placental abruption, chorioamnionitis and PROM in women with asthma. The results of the meta-analysis showed that women with asthma have a 23% increased risk of placenta previa and a 29% increased risk of placental abruption. The risk of chorioamnionitis was also increased with maternal asthma in studies that adjusted data for confounding factors such as maternal age, diabetes and pre-existing hypertension [21–23], smoking, education, race

and parity [21]. An increased risk of placental problems, particularly placenta previa, may be related to the increase in elective cesarean sections among women with asthma. Immunological changes characterizing pregnancy in asthmatic women may contribute to the increased risk for these maternal and fetal complications [53]. Diminished numbers of regulatory T cells (Tregs) in pregnancy were associated with immunological rejection of the fetus as well as pre-eclampsia and low fetal birth weight [54]. Furthermore, a substantial number of peripheral interferon (IFN)- γ producing T cells was negatively correlated with birth weight of newborns, suggesting that IUGR can be related to active, asthma-associated maternal immune reactions [55]. On the other hand, the abnormal asthma-dependent Th17 elevation and lower IFN- γ response following infection with influenza indicated a reduction in antiviral and regulatory immunity with increased inflammation during pregnancy, may relate to the increased susceptibility to respiratory viruses that cause severe asthma exacerbations during pregnancy [56,57].

Our study has some limitations. Firstly, analysis from observational studies cannot imply cause and effect, and we had fewer studies with prospective design. Secondly, in many studies, asthma was defined by self-report, and therefore, the lack of an objective definition of asthma as an inclusion criterion in the primary studies is a weakness of this analysis. Thirdly, in our analysis, bronchodilator use or not is a very generic description in these studies, because there are several different types of bronchodilators ranging from short acting beta-agonists (SABA) to long-acting beta-agonists (LABA) and muscarinic antagonists. Furthermore, patients may use only rescue medications during exacerbations or may use LABA as maintenance therapy. Muscarinic antagonists (ipratropium) are typically reserved for exacerbations. It would hinder from analyzing further effects of specific bronchodilators in maternal asthma on maternal and placental complications in pregnancy. Furthermore, limited studies did not allow the subgroup analyses for different bronchodilators. Fourthly, there was limited ability to account for the influence of confounding factors on the outcomes, such as socio-economic status, smoking history, preexisting hypertension and BMI because this information was not included in most primary studies. However, in some cases, we could analyze odds ratio data, which had been adjusted for confounders, and these confirmed results for cesarean delivery and placental abruption. In addition, some publications have described fetal sex-specific associations with placental function, but we did not consider fetal sex in this study. Finally, although we assessed active management based on author clinical involvement, this does not equate to adequate control, limiting our ability to evaluate the potentially important effect of asthma control on the outcomes evaluated.

Conclusion

Our study indicates that maternal and placental complications are more common among women with asthma. The association with gestational diabetes is particularly robust given that it is present in retrospective and prospective studies, in studies that adjust for other variables, shows no publication bias and is diminished in studies with active treatment of asthma.

The mechanisms involved in these associations require further study.

Contributors

Conception and design: G. W., V. E. M., M. S. and P. G. G. Analysis of the data: G. W., V. E. M., J. N., H. P., M. S., C. C., J. A. and P. G. G. Interpretation of the data: G. W., V. E. M., J. N., H. P., M. S., C. C., J. A. and P. G. G. Draft of the article: G. W., V. E. M., H. P. and P. G. G. Statistical expertise: G. W., V. E. M., H. P. and P. G. G. All the authors have read the manuscript, revised it critically for important intellectual content and approved the final version.

Declaration of interest

W. G. has received an APSR Research/Training Fellowship (2011), a scholarship as visiting Associated Professor at the University of Newcastle, Australia, and the ATS MECOR Program 2013 scholarship in Hanoi, Vietnam. All other authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary material available online

Supplementary Tables I–II

Table S1. Characteristics and reporting quality of included cohort studies on maternal and placental complications in pregnant women with asthma.

Study	Asthma Participants	Control Participants	Study Design	Data Source	Asthma Diagnosis	Active Asthma Management	Study Year	Study Country	Adjusted Data	Complications	Analysis	Quality Score
Acs 2005 ³²	N=757	N=37394	R	Database	Self report	No	1980-1996	Hungary	Maternal age, birth order, employment status, anti-asthmatic drugs, pregnancy supplements	Gestational diabetes	A	9
Alexander 1998 ³⁴	N=817	N=13709	R	Database	Database code	Unsure	1991-1993	Canada	Smoking, parity, age, pre delivery weight	Cesarean section; postpartum hemorrhage; gestational diabetes	B	8
Almeida 2010 ²⁹	N=299	N=4458	R	Database	Dr. Diagnosis	No	March to July, 2005	Brazil	No	Cesarean section	A	8
Bakhireva 2005 ⁴⁰	N=654	N=303	P	Interview, medical records	Dr diagnosis	No	1998-2003	USA/ Canada	No	Gestational diabetes	A	6
Breton 2009 ⁴¹	N=13100, 23% > 1	N=28042, 33% random	R	Database	Database code	No	1990-2002	Canada	Pregnancy induced	Placental abruption;	A	8

	pregnancy)	sample, 23% > 1pregnancy							hypertension, gestational diabetes, placental abruption, infection amniotic cavity	chorioamni onitis; gestational diabetes		
Clark 2007 ³	N=718	N=718	R	Database	Self report	No	2001-2003	UK	No	Emergency /elective/ce sarean section	A&B	9
Clifton 2009 ³⁹	N=1944	N=13977	R	Database	Database code	No	1995-1999	Australia	No	Antepartu m hemorrhag e; placenta previa; placental abruption; chorioamni onitis; gestational diabetes	A	7
Demissie 1998 ²¹ Demissie	N=2289	N=9156	R	Database -	Database code	No	1989-1992	USA	Maternal age, education, marital status,	Cesarean section; antepartum	A	9

1998 ⁴⁸									parity, race, diabetes, preexisting hypertension, smoking, alcohol use	hemorrhage; postpartum hemorrhage; placenta previa; placental abruption; chorioamnionitis; premature rupture of membranes; gestational diabetes		
Dombrowski 2004 ¹⁵	N=1739, 50% mild, 50% mod/severe	N=881	P	Clinical, Medical records	Self report	Yes Monthly visits including spirometry, data on symptom frequency, medication use and	1994-1999	USA	No	Postpartum hemorrhage	A & B	9

						exacerbations collected						
Dombrowski 2004 ⁴²	N=194 (Beclomethasone),	N=190 (Theophylline)	P	Clinical, Medical records	Self report	Albuterol inhalers, and beclomethasone or theophylline	1995-2000	USA	No	Cesarean delivery, chorioamnionitis, hemorrhage.	B	9
Eltonsy 2011 ³⁵	N=13117 (total) N=7182 SABA users, N=5935 SABA non-users	None	R	Database	Database code	Unsure	1990-2002	Canada	Maternal age, receipt of social assistance, area of residence, education level, hypertension, diabetes, epilepsy, uterine complications during pregnancy	Gestational diabetes	B	8
Enriquez 2007 ²⁵	N=9154, Asthma subjects more likely to smoke , more	N=131145	R	Database	Database code	No	1995-2003	USA	No	Cesarean section; antepartum hemorrhage; postpartum	A	9

	comorbidities than controls									hemorrhage; gestational diabetes		
Firoozi 2010 ³³	N=13007 Mild asthma (n=10737); moderate asthma (n=1618); severe asthma (n=652)	NA	R	Database	Database	Unsure	1990-2002	Canada	No	Gestational diabetes	B	9
Greenberger 1988 ³⁷	N=73 (total) N=26 (Emergency therapy) N=52 (No emergency therapy)	None	P	Clinical, case notes	ATS criteria	Unsure	1981-1987	USA	No	Gestational diabetes	B	8
Jana 1995 ¹³	N=182, 182 pregnancies	N=364, Matched for age & parity,	P	Clinical, case notes	ATS criteria	Yes Referred to specialist	1983-1992	Not stated	No	Elective/cesarean section;	A	8

	s in 158 women, 2 x twins	delivered within 48hrs of asthma cases, 6 x twins				clinic - included instruction on continuing asthma meds, exacerbation management and regular assessment by chest physician				antepartum hemorrhage; premature rupture of membranes ; gestational diabetes		
Kallen 2007 ²⁷	N=24369 N=24750 N=24749 Multiple pregnancies included	N=835848 N=849254 N=849127 Multiple pregnancies included	R	Database	Self report	No	1995-2004	Sweden	Year of birth, maternal age, parity, smoking, years of unwanted childlessness	Cesarean section; antepartum hemorrhage; placenta previa; placental abruption; premature rupture of	A	9

										membranes ; gestational diabetes;		
Karimi 2008 ²⁸	N=76	N=152	R	Unsure	Not stated	No	Not stated	Iran	No	Cesarean section	A	4
Lao 1990 ¹⁹	N=87	N=87, matched for age & parity	R	Case Notes	Not stated	Yes Asthma subjects closely followed up in antenatal clinic	1984-1987	Hong Kong	No	Emergency /elective/ce sarean section; postpartum hemorrhag e	A & B	8
Liu 2001 ²²	N=2193, Likely to represent non severe asthma	N=8772	R	Database	Database code	No	1991-1992 & 1995- 1996	Canada	Maternal age, diabetes, preexisting hypertension	Cesarean section; anteartum hemorrhag e; postpartum hemorrhag e; placenta previa; placental abruption; chorioamni onitis;	A	8

										premature rupture of membranes		
Macmullen 2010 ³⁰	N=7777	N=31108	R	Database	Database code	No	2001	USA	Maternal age, gestational diabetes, preexisting diabetes, hypertension.	Cesarean section; antepartum hemorrhag e; postpartum hemorrhag e; placenta previa; placental abruption; chorioamni onitis; premature rupture of membranes ; gestational diabetes	A	8
Martel 2009 ³¹	N=8226 mild asthma (n=6805);	NA	R	Database	Database code		1990-2002	Canada	No	Emergency cesarean section; gestational	B	7

	moderate to severe asthma (n=1421)									diabetes		
Mihrshahi 2003 ¹⁸	N=340	N=271, 21 without asthma were using medications	P	Clinical, medical records	Dr diagnosis	No	1991-1992 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension	Cesarean section; gestational diabetes	A	8
Minerbi-Codish 1998 ¹⁷	N=101	N=77, matched for age & ethnicity	P	Interview, medical records	Self report	No	1993-1994	Israel	No	Cesarean section	A & B	8
Murphy 2005 ⁴⁹	N=146 (total) N=52 (Exacerbation) N=92 (No Exacerbation)	None	P	Clinical, medical records	Dr diagnosis	Unsure	1997-2003	Australia	No	Emergency cesarean section	B	7
Murphy 2007 ¹⁶	N=119	N=84	P	Clinical, medical records	Dr diagnosis	Yes Asthma education provided by	1998-2003	Australia	No	Cesarean section	A	6

						asthma educator, access to physician for exacerbatio ns						
Norjavaa ra 2003 ⁴³	N=11186 (total) N=7719 (asthma drugs other than CS) N=3364 (ICS only) N=103 (OCS + ICS)	None	R	Database	Use of anti- asthmatic drugs	Unsure	1995-1998	Sweden	No	Cesarean section	B	7
Perlow 1992 ²⁰	N=81	N=130, matched for time of delivery – next 2 deliveries after asthma cases	R	Database and patient chart review	Dr diagnosis	No	1985-1990	USA	No	Cesarean section; gestational diabetes	A	5

Schatz 1995 ⁴⁵ , Schatz 1988 ³⁸ , Schatz 1991 ¹²	N=486 N=360 N=294	N=486 N=295 N=294 matched for age, parity, smoking, delivery date	P	Clinical, medical records	Dr diagnosis, objective lung function	Yes Monthly assessment in the allergy clinic including symptom and medication diaries and treatment adjustment	1978-1989 1978-1984 1978-1984	USA	No	Cesarean section; postpartum hemorrhag e; gestational diabetes	A	9
Sheiner 2005 ²⁴	N=1963	N=137205	R	Database	Database code	No	1998-2002	Israel	No	Cesarean section; antepartum hemorrhag e; postpartum hemorrhag e; placenta previa; placental abruption; premature rupture of	A	9

										membranes		
Silverman 2005 ³⁶	N=313 (total) N=196 Budesonide N=117 Placebo	None	RCT	Pregnancy specific form	Lung function	Unsure	1996-1998	32 countries	No	Cesarean section	B	7
Sobande 2002 ⁴⁴	N=88, Acute asthma	N=106	P	Medical records	Dr diagnosis	Yes Hospital admission for asthma – managed by specialist and treated	1997-2000	Saudi Arabia	No	Gestational diabetes	A	7
Stenius Aarniala 1988 ¹¹	N=181, 198 pregnancies	N=198, matched for age, parity & time of delivery	P-asthma R-control	Clinical, medical records	ATS criteria	Yes Seen in dept of pulmonary medicine including regular symptom assessment and peak	1978-1982	Finland	No	Emergency /elective/cesarean section, placental abruption; premature rupture of membranes ; gestational	A	7

						flow monitoring				diabetes		
Stenius- Aarniala 1995 ¹⁴ ; Stenius- Aarniala 1996 ⁴⁶	N=504	N=237, matched for age & parity	P- asthma, R- control	Clinical, medical records	ATS criteria	Yes Women referred to pulmonary medicine departments for regular checkups during pregnancy. Asthma follow-up and treatment provided by study authors.	1982-1992	Finland	No	Emergency /elective/ce sarean section; antepartum hemorrhag e; placental abruption; premature rupture of membranes ; gestational diabetes	A & B	8
Tamasi 2005 ⁴⁷	N=48	N=18, similar age & gestational age	P	Clinical	Not stated	Yes Referred to 'Asthma ambulance' including history,	Not stated	Hungary	No	Gestational diabetes	A	6

						asthma medication use and treatment adjustment during the pregnancy.						
Tata 2007 ²⁶	N=37585, Includes multiple pregnancies - similar between groups	N=243434, Includes multiple pregnancies - similar between groups	R	Database	Database code	No	1998-2004	UK	Maternal age, smoking, BMI	Cesarean section; antepartum hemorrhage; postpartum hemorrhage; placenta previa; placental abruption; gestational diabetes	A	9
Wen 2001 ²³	N=8672	N=34688	R	Database	Database code	No	1989-1990 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension, cesarean also	Cesarean section; antepartum hemorrhage;	A	7

									adjusted for pregnancy complications	postpartum hemorrhag e; placenta previa; placental abruption; chorioamni onitis; premature rupture of membranes ; gestational diabetes		
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R=Retrospective; P=Prospective.

Table S2. Exposure definitions for analysis B of asthma subgroups.

Study	Exacerbation Definition	Mild Asthma Definition	Moderate/Severe Asthma Definition
Greenberger 1988 ³⁷	Asthma requiring epinephrine and OCS in the outpatient service, emergency department or hospital		
Stenius-Aarniala 1996 ⁴⁶	Asthma which was not controlled by the woman's usual rescue medication and was treated as an emergency		
Murphy 2005 ⁴⁹	Hospital admission, emergency department presentation, unscheduled doctor's visit or course of oral steroids		
Dombrowski 2004 ¹⁵		Asthma symptoms in the prior 6 months, asthma symptoms fewer than 8 days in prior 4 weeks, FEV1 $\geq$ 80% predicted, not taking daily asthma medication	Asthma symptoms on 8 or more days during the prior 4 weeks not attributable to upper respiratory infection, FEV1 $<$ 60-79% predicted, use of one or more daily medications which may include oral corticosteroids in severe asthmatics.
Minerbi-Codish 1998 ¹⁷		Treated with bronchodilators as needed. Not receiving any other medical treatment for asthma, and not hospitalized with asthma during pregnancy.	Moderate: Treated regularly with ICS as preventative treatment, and with bronchodilators regularly or as needed. Occasionally awakened at night by asthma or experienced chest tightness with physical activity. Not hospitalized with asthma during pregnancy.

			Severe: Treated regularly with preventative treatment, and with courses of systemic corticosteroids during deterioration. Included those with permanent systemic corticosteroid treatment, or who visited the emergency department or were hospitalized with asthma during pregnancy.
Martel 2009 ³¹		SABA use less than 4 doses/week ICS less than 500 mcg/day	Higher doses of ICS combined with other asthma controller medications (such as theophylline, LABA, leukotriene receptor antagonists)
Firoozi 2010 ³³		ICS 0-500mcg/day and no additional controller therapy or 0-250 mcg/day and additional controller therapy No moderate to severe asthma exacerbation No more than 3 doses of SABA over a 12 month period	Moderate: ICS >500 mcg/day with no additional controller therapy or doses >250 mcg/day for those receiving additional controller therapy OR >4 doses SABA per week over a 12 month period and moderate to severe exacerbation Severe: ICS > 1000 mcg/day OR >10 doses SABA per week and moderate to severe exacerbation