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 1975 and March 2012 were considered for inclusion. 40 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 (CI) 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; pregnancy; meta-analysis.

Abstract word count: 213

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[7], 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, socioeconomic 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 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) 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, 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 relative risks 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 ten 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 ten 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). 40 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 paper 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.

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],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 analysed according to asthma management sub-categories, there was a significantly increased risk of 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 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 relative risk 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 relative risks 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]). 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 which 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 premature rupture of membranes (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 cesarean delivery, and twice the risk of elective C section. The number of studies which investigated cesarean 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 which 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 cesarean delivery. Although generally C section is more likely to be indicated for obstetric reasons than asthma, asthma is associated with a number of conditions which may contribute to C section, such as maternal obesity, placental complications (as already mentioned) and 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 cesarean delivery but not emergent cesarean delivery is needed to be further studied.

In the Swedish Medical Birth Registry study, the risk of cesarean delivery remained after excluding women with medical conditions known to be associated with cesarean 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 which 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, was 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 body mass index [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 relative risk 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 11β-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 which 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 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 fetal growth restriction (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 criteria 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 analysing further effects of specific bronchodilators in maternal asthma on maternal and placental complications in pregnancy. What's more, limited studies didn't 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 socioeconomic status, smoking history, pre-exiting hypertension and BMI because this information was not included in most primary studies. However, in some cases we could analyse 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: WG, MVE, SM, GPG. Analysis of the data: WG, MVE, NJ, PH, SM, CC, AJ, GPG. Interpretation of the data: WG, MVE, NJ, PH, SM, CC, AJ, GPG. Draft of the article: WG, MVE, PH, GPG. Statistical expertise: WG, MVE, PH, GPG. All the authors have read the manuscript, revised it critically for important intellectual content, and approved the final version.

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Legends

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

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

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	18450/88475	209622/1376202	1.31 [1.22, 1.39]	90.8%
Prospective	8	714/3479	416/2410	1.26 [1.09, 1.46]	24.6%
Retrospective	13	17736/84996	209206/1373792	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	2956/99700	16437/1304675	1.39 [1.17, 1.66]	88.4%
Prospective	9	173/4239	89/2862	1.16 [0.90, 1.50]	0.0%
Retrospective	10	2783/95461	16348/1301813	1.45 [1.18, 1.78]	93.9%
Antepartum hemorrhage	11	1389/86365	14057/1382224	1.25 [1.10, 1.42]	71.3%
Prospective	2	13/686	23/601	0.61 [0.12, 2.13]	74.2%
Retrospective	9	376/85679	14057/1382224	1.29 [1.17, 1.43]	60.0%
Postpartum hemorrhage	10	1436/61552	6161/533662	1.29 [1.18, 1.41]	39.1%
Prospective	2	135/2099	58/1176	1.09 [0.56, 2.12]	63.9%
Retrospective	8	1301/59453	6103/532486	1.30 [1.18, 1.42]	41.3%
Placenta previa	8	250/76525	3470/1251079	1.23 [1.07, 1.40]	0.0%
Prospective	NA	NA	NA	NA	NA
Retrospective	8	250/76525	3470/1251079	1.23 [1.07, 1.40]	0.0%
Placental abruption	11	966/90327	6649/1279121	1.29 [1.14, 1.47]	44.8%
Prospective	2	7/702	3/435	1.43 [0.37, 5.52]	0.0%
Retrospective	9	959/89625	8646/1279121	1.29 [1.13, 1.48]	54.1%
Chorioamnionitis	7	1425/37714	2855/126624	1.45 [0.96, 2.22]	97.1%
Prospective	1	103/1739	44/881	1.19 [0.84, 1.67]	NA
Retrospective	6	1322/35975	2811/125743	1.50 [0.94, 2.40]	97.6%
Premature rupture of membrane	9	1897/48147	24817/1057576	1.21 [1.07, 1.37]	74.6%
Prospective	3	34/884	42/799	0.91 [0.52, 1.58]	20.0%
Retrospective	6	1863/47263	24775/1056777	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	17855/85437	209252/1374138	1.31 [1.22, 1.42]	94.0%
	Postpartum hemorrhage	6	1298/59366	6102/532399	1.29 [1.18, 1.42]	47.4%
	Gestational diabetes	12	2830/96455	16368/1302385	1.45 [1.20, 1.76]	92.6%
			Asthma group with characteristic	Asthma group without characteristic		
Bronchodilator use	Cesarean section	3	100/466	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%
Asthma severity (moderate to severe)	Cesarean section	3	538/2339	1503/7727	1.19 [1.09, 1.31]	0.0%
	Emergency cesarean section	2	203/2287	764/7678	1.09 [0.94, 1.27]	0.0%
	Gestational diabetes	3	384/4557	1392/18415	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%

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 vs prospective design	21	1.04 (0.11)	0.702
	Active vs non active management	21	1.06 (0.12)	0.608
	Country vs 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 vs 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 vs prospective design	19	1.20(0.25)	0.389
	Active vs no active management	19	0.77 (0.18)	0.286
	Country vs 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 vs 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