Effects of Asthma Severity, Exacerbations and Oral Corticosteroids on Perinatal Outcomes

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Potential Conflicts of Interest:

Jennifer A. Namazy, MD: Genentech

Peter G Gibson, MBBS, FRACP: Glaxo Smith Kline, Boehringer Ingelheim, National Health and Medical Research Council

Christina Chambers, PhD, MPH: Amgen, Abbott, Apotex, Sandoz, Barr, Heritage, Kali, Bristol Myers Squibb, Sanofi Aventis, Sanofi Pasteur

Michael Schatz, MD: Aerocrine, Glaxo Smith Kline, Genentech, Merck, Amgen.

TOTAL WORD COUNT- 3184
Abstract

Objective:
This systematic review and meta-analysis sought to investigate if asthma exacerbations, oral corticosteroid use, or asthma severity are associated with prematurity and intrauterine growth restriction.

Methods:
Cohort studies published between 1975 and March 11, 2012 were considered for inclusion. 138 publications were identified for possible inclusion, and 9 papers met the inclusion criteria, by reporting perinatal outcomes of interest (low birth weight (<2500gm), preterm birth (< 37 weeks gestation unless otherwise stated), and small for gestational age (<10th percentile for gestational age and sex) in groups of asthmatic patients stratified by history of exacerbations, oral corticosteroid use, or asthma severity.

Results:
Maternal asthma exacerbations and oral corticosteroid use had a significant effect on outcomes including: low birth weight (RR 3.02, 95%CI[1.87,4.89]) and RR 1.41,95%CI[1.04,1.93], respectively) and preterm delivery (RR 1.54, 95%CI[0.89,2.69] and (RR 1.51,95%CI[1.15,1.98], respectively). Moderate to severe asthma during pregnancy was associated with an increased risk of small for gestational age (RR 1.24, 95%CI[1.15,1.35]) and low birth weight (RR 1.15,95%CI[1.05,1.26]) infants.

Conclusion:
These data suggest that asthma exacerbations, oral corticosteroid use, or asthma severity defined as moderate to severe may be associated with preterm delivery, low birth weight, and small for
gestational age. Further studies on the effect of maternal asthma control on perinatal outcomes are warranted.

**Key Words:**
Asthma, pregnancy, preterm delivery, small for gestational age, low birth weight, oral corticosteroid

**Abbreviations:**
SGA – small for gestational age
LBW – low birth weight
OCS- oral corticosteroid

**Introduction**

Asthma is the most common medical condition to affect pregnancy with a prevalence between 8 and 13 % worldwide (1-3). It has been suggested that asthma may have an effect on pregnancy outcomes, and also that pregnancy may affect the course of asthma (4), but the published data have been conflicting. For this reason we recently conducted a meta-analysis to investigate whether maternal asthma is associated with an increased risk of pregnancy and neonatal complications. We found that women with asthma during pregnancy are at an increased risk of perinatal complications including low birth weight (LBW), preterm delivery and small for
gestational age (SGA) (5) These findings were recently supported by a Canadian population-based cohort study of 40,788 pregnancies (6).

About 70% of all low birth weight infants are a result of preterm delivery before 37 completed weeks of pregnancy. Therefore, the observed increase in preterm delivery in pregnant asthmatics may explain most of the increased prevalence of low birth weight in their infants. However, small for gestational age, most often a result of intrauterine growth restriction, may occur in either term or preterm infants and also accounts for some low birth weight infants.

Mechanisms for these adverse perinatal outcomes have not been defined. Several studies have reported a relationship between increased asthma severity or decreased asthma control and increased risk of low birth weight, small for gestational age, and preterm delivery (7-19). One recent meta analysis found that pregnant asthmatic women with a history of severe exacerbation during pregnancy are at a significantly increased risk of perinatal complications including low birth weight (20). The use of asthma medications such as oral corticosteroids during pregnancy may also play a potential role in leading to preterm delivery or low birth weight infants (21) and have been suggested as contributing factors by several large cohort studies (10, 14).

To better understand potential mechanisms involved in the increased risk of prematurity and intrauterine growth restriction observed in mothers with asthma we have undertaken a systematic review of the literature and meta-analyses to investigate whether maternal asthma severity, history of exacerbation or oral corticosteroid use during pregnancy are associated with the risk of preterm, low birth weight, or small for gestational age infants.
Methods

Systematic review of the literature-Search strategy

English language studies published between 1975 (when inhaled corticosteroids were introduced) and March 2012 were identified for possible inclusion from Medline (n=1642), Embase (n=1755), CINAHL (n=417), and Cochrane Central Register of Controlled Trials (n=75), using search terms ((asthma or wheeze) and (pregnan* or perinat* or obstet*)). An update was conducted and the search for the update was Jan 2009-March 2012 to ensure no articles were missed. The numbers for the update were: Medline (n=681), Embase (n=624), CINAHL (n=84), and Cochrane Trials Register (n=14). All identified abstracts were independently assessed by two reviewers. The full text version of each potential article was obtained for assessment by two independent reviewers to establish whether it met the inclusion criteria.

Inclusion criteria

Articles were included if they were cohort studies that contained data comparing perinatal outcomes of interest (see below) in groups of asthmatic patients stratified by history of
Exacerbations oral corticosteroid use, or asthma severity. Asthma was defined as physician-diagnosed asthma (whether confirmed or subject self-report), or an asthma diagnosis as coded in a database, or asthma fulfilling American Thoracic Society criteria. Women with asthma were further classified by symptom severity according to national and international guidelines (Global Initiative for Asthma or National Asthma Education Program Working Group on Asthma and Pregnancy) (14) or number of medications used to control asthma symptoms (one drug = mild, two and three drugs = moderate/severe) (22) or a validated index combining medication use, and markers of exacerbation (23, 24) (Table I). Exacerbations of asthma were defined (Table II) as symptoms requiring medical interventions such as hospitalization, emergency department visits, other unscheduled urgent visits to the doctor, or the use of emergency treatment. In two of the studies, emergency treatment included the use of oral corticosteroids (8, 25). Most studies included exacerbations occurring anytime during pregnancy with the exception of one study, which limited exacerbations to the first trimester only (14). Perinatal outcomes of interest for this article included low birth weight (<2500gm), preterm birth (<37 weeks gestation unless otherwise stated), and small for gestational age (<10th percentile for gestational age and sex).

Description of studies

138 publications were identified for possible inclusion in the review. 9 papers describing 7 prospective and 2 retrospective cohort studies met the inclusion criteria (Table III). 95 papers were excluded for the following reasons: no asthma subgroups (n=29), poorly defined asthma subgroups (n=6), asthma subgroups that did not meet our inclusion criteria (n=24), no asthma comparison group (n=10), study published after 1975 but conducted prior to 1975 (n=2), cross-
sectional survey (n=3), abstract only (n=10), no perinatal outcomes reported (n=16), review article (n=6), case control study design (n=15, data presented as odds ratio (OR) only (n=4), retracted article (n=1) and overlapping data with another study (n=3) (Table IV)

_Data Extraction_

Data was extracted using a standardized form by one reviewer and checked by a second reviewer. Any discrepancies were discussed by the investigators in order to reach a consensus. Study authors were contacted to clarify an outcome definition where necessary.

Data were extracted for: study design, study characteristics (including year, country of study), subject characteristics (including gestational age at recruitment, subject exclusions, maternal age, body mass index, smoking, socioeconomic status, prenatal care, race/ethnicity, co-morbidities), asthma diagnosis, severity, medication management, exacerbations and perinatal outcome data for asthma subgroups (mostly as n[\%] or mean[SD])

Study quality was assessed independently and scored by two reviewers using the Newcastle-Ottawa Scale (NOS)(26). The NOS is a validated tool for assessing the quality of non-randomized studies including cohort and case-control studies and has a maximum score of 9. The mean quality score of included studies (8.3, Table III) was ranked as good.

_Meta-Analysis_
The meta analyses conformed to standard methodological guidelines for observational studies(27) The relative risk of the perinatal outcome was examined in subgroups of women with asthma stratified by severity (mild versus moderate-severe), gestational asthma exacerbations (expressed as a yes/no variable) and exposure to oral corticosteroids (expressed as a yes/no variable) using Review manager software (Review Manager Version 4.2.7 The Cochrane Collaboration 2004. Wintertree Software Inc. Available at: http://www.cc-ims.net/RevMan/download.htm.). For dichotomous outcomes the relative risk with 95% confidence interval was calculated using a fixed effects model. Heterogeneity was examined using the Chi-squared test (P<0.1 considered significant heterogeneity) and the I- square percentage (I- square ≥ 60% considered significant heterogeneity, RevMan).
Results

RELATIONSHIP BETWEEN ASTHMA EXACERBATIONS AND PERINATAL OUTCOME

Preterm Delivery

Data on preterm delivery was reported in 5 prospective studies (7, 8, 13, 17, 18) of 179 subjects experiencing exacerbations during pregnancy and 1035 subjects without exacerbations. The data from two papers from Fitzsimons and Greenberger published in 1986 and 1988, respectively, were overlapping, and so the data from the 1988 paper, which contained a larger group of subjects was included here (and for subsequent analyses reported below) (17). In the study from Jana et al. there was a comparison of “mild versus severe asthma” which we translated to “no exacerbation versus exacerbation”, since their definition of “severe” asthma was asthma which required emergency hospitalization for symptoms. Overall, there was a non-significant trend of increased preterm delivery in asthmatics with exacerbations during pregnancy (RR 1.54[0.89,2.69]). There was no significant heterogeneity among studies [I2 =0\%,P>0.1].
**Low Birth Weight**

Data on low birth weight was included in 4 prospective studies (8, 13, 17, 18) with 147 subjects with an exacerbation during pregnancy and 747 subjects without an exacerbation during pregnancy. There was a significantly increased risk of low birth weight infants of those subjects experiencing asthma exacerbation during pregnancy (RR 3.02[1.87,4.89]). There was no significant heterogeneity among studies [I² =0%, P>0.1] (Figure 1).

**Small for Gestational Age**

Data on small for gestational age (SGA) infants was included in 2 studies(17, 18) with 80 subjects experiencing exacerbations during pregnancy and 487 subjects without exacerbations. There was no significant increased risk of SGA infants in those asthmatics experiencing exacerbation during pregnancy compared to those with no severe exacerbations during pregnancy (RR 0.78[0.25,2.48]). However significant heterogeneity was present (I² = 71.1%, p=0.06).

**RELATIONSHIP BETWEEN ORAL CORTICOSTEROID USE AND PERINATAL OUTCOME**

**Preterm Delivery**
Data on preterm delivery was included in 2 prospective studies (18, 21) with 267 subjects who used oral corticosteroids during pregnancy compared with 2341 subjects who did not use oral corticosteroids during pregnancy. Overall, oral corticosteroid use increased the relative risk of preterm delivery (RR 1.51, 95%CI [1.15, 1.98]), with no significant heterogeneity between studies [I² = 0%, P > 0.1] (Figure 2).

**Low Birth Weight**

Data on low birth weight was included in 2 prospective studies (18, 21) with 267 subjects using oral corticosteroids during pregnancy and 2341 subjects who did not use oral corticosteroids. Overall, there was a significant increased risk of low birth weight infants to those women using oral corticosteroids during pregnancy (RR 1.41, 95%CI [1.04, 1.93]). There was no heterogeneity between studies (Figure 3).

**Small for Gestational Age**

There were 2 prospective studies (18, 21) with 267 subjects who used oral corticosteroids during pregnancy and 2341 subjects who did not use oral corticosteroids during pregnancy. Overall, there was no significant increased risk of SGA among women using oral corticosteroids during pregnancy [RR 0.81, 95%CI [0.48, 1.34]].

**RELATIONSHIP BETWEEN ASTHMA SEVERITY AND PERINATAL OUTCOMES**
**Preterm Delivery**

There were 3 studies reporting on the effect of maternal asthma severity on preterm delivery. One retrospective(22) and one prospective study(14) reported early preterm delivery <32 weeks completed gestation as an outcome. Overall, the risk of early preterm delivery was not increased in women with moderate/severe asthma compared to women with mild asthma (RR 1.08 95%CI[0.4,1.39]).

Two retrospective (22) (23) and 1 prospective study(14) reported preterm delivery < 37 weeks gestation. Overall, there was no increased risk of preterm delivery in moderate/severe versus mild asthmatic women (RR 1.00, 95%CI[0.93,1.09]).

**Low Birth Weight**

Two retrospective studies (22, 23) reported low birth weight among women with mild and moderate/severe asthma. There was an increased risk of low birth weight in moderate/severe versus mild asthmatic women (RR 1.15, 95%CI [1.05, 1.26]).

**Small for Gestational Age**

There were two retrospective studies(22, 23) and one prospective study(14) with 13400 subjects with moderate/severe asthma and 25334 subjects with mild asthma severity. Meta-analysis comparing mild to moderate/severe asthmatics demonstrated a significantly increased risk of
SGA in infants of subjects with asthma classified as moderate/severe compared to those with mild asthma during pregnancy [RR 1.24, 95%CI[1.15,1.35]). There was no significant heterogeneity between studies (I² =20.9%,P>0.1). (Figure 4).
Discussion

Previous studies as well as a recent meta-analysis (5) have shown that pregnancies in women with asthma when compared with pregnancies in non-asthmatic women are at an increased risk of preterm birth, low birth weight, and small for gestational age. Up until now it has been unclear what mechanisms are responsible for these observations. Our results show that exacerbations and oral corticosteroid use during pregnancy are associated with an increased incidence of preterm and low birth weight infants while moderate to severe asthma during pregnancy is associated with an increased risk of low birth weight and small for gestational age infants (Table IV). These results suggest that acute asthma events (exacerbations and oral corticosteroid use) increase the risk of prematurity while more chronic severity increases the risk of intrauterine growth restriction.

A recent population-based cohort study published after the end of our meta-analysis inclusion period of over 40,000 pregnancies found that asthmatic women with a history of exacerbation defined as acute care for asthma recorded in the databases were more likely to have a LBW or preterm infant than non-asthmatic women (5), agreeing with the results of this meta-analysis. However, this study also found an increased risk of small for gestational age infants in asthmatic women with exacerbations compared to non-asthmatic women. This finding is at variance with our results, but may be related to the different comparison groups used in their study (non-asthmatic women) versus our meta-analysis (asthmatic women without exacerbations).
Another recent study of over 9000 pregnant asthmatic women showed that those women with a hospitalization or emergency department visit had an increased risk of low birth weight infants (28). Murphy et al reported in a meta-analysis of 855 asthmatics that there was an increased risk of low birth weight infants but not preterm delivery (20) associated with exacerbations during pregnancy. For our meta-analysis, the cause of asthma exacerbations was unknown in all studies except one (8), whose authors found that triggers included non-adherence to inhaled corticosteroid medications in about one third and viral infection another third. Stenius-Aarniala et al found 31 of the 45 subjects with a history of exacerbation during pregnancy were not using inhaled corticosteroids (7) Two studies also examined potential maternal risk factors for asthma exacerbations, such as age, parity, smoking, and body mass index, and found no significant differences between women who had a severe exacerbation and those who did not (8, 18). An interesting observation by Greenberger et al (17) was that while subjects with untreated status asthmatics had a higher risk of adverse perinatal outcomes, those subjects who were treated for exacerbations with inhaled or oral corticosteroids had much more favorable outcomes. In our analysis, the relative risk of low birth weight in oral corticosteroid users (RR 1.41) was approximately half that of women with severe exacerbations (RR 3.02). A possible mechanism for the effect of severe asthma or exacerbations on perinatal outcomes includes a direct effect of fetal hypoxia on fetal growth, or indirect effects of placental insufficiency (29), both of which could presumably be mitigated by prevention or possibly expeditious treatment of asthma exacerbations.

When we examined the potential effect of oral corticosteroid use on perinatal outcomes, we found that pregnant asthmatic women who used oral corticosteroids during pregnancy had an
increased risk of preterm delivery (<37 completed weeks gestation) and low birth weight infants. There have been several cohort studies that have shown significant effects of maternal asthma on preterm delivery that may be related to oral corticosteroid use. Pregnant asthmatics taking a mean daily dose of 8mg of prednisone a day had an increased risk of preterm delivery (30). Dombrowski et al found a significant effect of severe asthma (FEV1<60% and/or oral corticosteroid use in the 4 weeks prior to enrollment) on preterm delivery with an adjusted OR of 2.2, 95% CI 1.2,4.2 (14). Bracken et al studied 873 pregnant women with a history of asthma (of whom 778 had no physician diagnosis, only asthma symptoms) and showed increased odds of preterm delivery with the use of oral corticosteroids (adjusted OR 1.11, 95%CI 1.03,1.18). This particular study was excluded from our meta-analysis since the asthma cohort may have contained non-asthmatic subjects. Perlow et al, compared 31 steroid dependent asthmatics to 50 non-steroid dependent asthmatics and found a significantly increased risk of preterm delivery and low birth weight in the group dependent on oral corticosteroids (15).

Since oral corticosteroids are most commonly used short-term to treat exacerbations (which the current meta-analysis shows increases the risk of low birth weight), it would seem that some or even most of the risk of prematurity associated with oral corticosteroids may be related to their being a marker for asthma exacerbations. One study did report an association of oral corticosteroids with prematurity after adjusting for exacerbations and FEV1. Thus a direct effect of oral corticosteroids cannot be excluded, but it will probably require studies in pregnant patients without asthma to define such a direct effect without confounding by asthma exacerbations.
Aside from oral corticosteroids, other asthma medications could potentially increase the risks of prematurity or intrauterine growth restriction. When specific medication use was examined there were an insufficient number of articles to include in this meta-analysis. However, the existing data do not suggest that asthma medications including beta-agonists, inhaled corticosteroids, or theophylline contribute to the increased risk of preterm delivery, low birth weight or small for gestational age in the pregnancies of asthmatic women. Further studies are needed to address the safety of these medications during pregnancy.

Our results specifically show that pregnant asthmatics with moderate to severe persistent asthma have an increased risk of low birth weight and small for gestational age infants relative to pregnant asthmatics with mild asthma. This is consistent with several prior observations suggesting that pregnant women with lower FEV 1 or severe asthma have an increased risk of adverse perinatal outcomes (31) which include small for gestational age (16, 32, 33). Dombrowski et al adjusted for potential confounders such as smoking, race, socioeconomic status, and found that there remained an increased risk of small for gestational age in moderate to severe asthmatics (14). We were unable to separate who of the moderate to severe asthmatics had suboptimally controlled asthma. Increased asthma severity may lead to an increased risk of asthma exacerbations as well as more difficult to control chronic asthma, with potential chronic hypoxia. Chronic hypoxia associated with high altitude pregnancy has been associated with an increased risk of intrauterine growth restriction(34).

It can be hypothesized that better control of asthma during pregnancy will lead to a reduction in asthma exacerbations and thus fewer adverse perinatal outcomes. In support of this, a previous
meta-analysis found that active asthma management (defined as investigators of a study being involved in the management and treatment of enrolled subjects with asthma) might be effective in reducing the occurrence of preterm labor and preterm delivery (5). This observation may be explained by active asthma management reducing exacerbations, or courses of oral corticosteroids, both of which have been implicated in some studies as contributing to the risk of preterm delivery (20).

Limitations of this meta-analysis include inadequate power based on still limited sample sizes of studies, differences in definitions between studies of severity and exacerbations, and the inability to control for potential confounding variables. Potential confounders such as socioeconomic status, ethnicity, and smoking history may have explained some of the observed heterogeneity. However, this information was not included in most studies.

There are significant clinical implications of this study. Because women with moderate to severe asthma or exacerbations of asthma during pregnancy were at a higher risk of having a premature, low birth weight infant, and/or small for gestational age infant, our results provide a rationale for making the control of asthma a priority in the management of asthma during pregnancy. With adequate control of asthma, there will be a reduction in exacerbations, need for systemic corticosteroids, as well as maternal and fetal hypoxia, which could lead to improvements for the neonate. As a result this could improve outcomes including prematurity and intrauterine growth restriction. Current guidelines recommend that the goal of treatment for the pregnant asthma patient is to provide optimal therapy to maintain control of asthma for maternal health and quality of life. As in the non-pregnant asthmatic, this includes minimizing symptoms, exacerbations, limitations in activities and need for rescue medications.
In conclusion, the current meta-analysis indicates that those pregnant asthmatics with asthma exacerbations, need for oral corticosteroids, and moderate to severe asthma are at an increased risk of preterm delivery, low birth weight and small for gestational age. We consider this analysis to have important implications because it suggests that optimal disease control may reduce these adverse perinatal outcomes. Further studies will be necessary to show convincingly that well-controlled asthma is not associated with adverse perinatal outcomes.

Acknowledgements

Wang Gang for his assistance


Table I: Definition of "severity" used in studies addressing the associations between asthma severity and perinatal outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Dombrowski\(^{14}\)    | Mild: asthma symptoms in the prior 6 mos  
  asthma symptoms fewer than 8 days in prior 4 weeks  
  FEV1\(\geq80\)% predicted  
  Not taking daily asthma medication  
  Moderate/Severe: Asthma symptoms on 8 or more days during the prior 4 weeks not attributable to a URI  
  FEV1\(<60-79\)% predicted  
  Use of one or more daily medications which may include oral corticosteroids in severe asthmatics.                                                                                      |
| Kallen\(^{22}\)        | Mild: 1 asthma drugs  
  Moderate/Severe: 2 or more asthma drugs                                                                                                                                                                                                                                                                                                 |
| Firoozi \(^{23,24}\)   | Asthma severity index:  
  Mild: ICS 0-500mcg/d* and no additional controller therapy\(\text{T}\) or 0-250 mcg/d and additional controller therapy  
  No moderate to severe asthma exacerbation\(\text{S}\)  
  No more than 3 doses of SABA over a 12 month period  
  Moderate: ICS >500 mcg/d with no additional controller therapy or doses >250 mcg/d  
  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/d OR >10 doses SABA per week and moderate to severe exacerbation |
Table II: Definition of "exacerbation" used in studies addressing the associations between asthma exacerbations and perinatal outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy⁸</td>
<td>hospital admission, emergency department presentation, unscheduled doctor's visit, or course of OCS</td>
</tr>
<tr>
<td>Stenius-Aarniala⁷</td>
<td>not controlled by the patient's normal rescue medication and which was treated as an emergency (74.4% OCS)</td>
</tr>
<tr>
<td>Jana¹³</td>
<td>requiring emergency services and/or hospitalization.</td>
</tr>
<tr>
<td>Schatz¹⁸</td>
<td>requiring emergency therapy with nebulized bronchodilators in the clinic or emergency room</td>
</tr>
<tr>
<td>Greenberger¹⁷</td>
<td>requiring epinephrine and OCS in the outpatient service, emergency room or hospital</td>
</tr>
</tbody>
</table>

OCS= Oral Corticosteroids
Table III: Summary of Studies addressing effect of asthma exacerbations, oral corticosteroid use, and asthma severity on perinatal outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Asthma Subjects</th>
<th>Year</th>
<th>Region</th>
<th>Study Design</th>
<th>Quality Score</th>
<th>Severity</th>
<th>OCS</th>
<th>Exacerbation</th>
<th>Outcomes</th>
<th>Data Source</th>
<th>Active Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schatz(^{21})</td>
<td>Total=2123</td>
<td>2004</td>
<td>USA</td>
<td>P</td>
<td>8</td>
<td>Y</td>
<td>preterm, LBW, SGA</td>
<td>Clinical, case notes</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCS Subgroup=185</td>
<td></td>
<td></td>
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<tr>
<td>Dombrowski(^{4})</td>
<td>N=1739</td>
<td>2004</td>
<td>USA</td>
<td>P</td>
<td>9</td>
<td>Y</td>
<td>preterm, SGA</td>
<td>Clinical collection, medical records</td>
<td>Y</td>
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<tr>
<td>Mod/Sev Subgroup=866</td>
<td></td>
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<tr>
<td>Kallen(^{22})</td>
<td>N=23988</td>
<td>2007</td>
<td>Sweden</td>
<td>R</td>
<td>9</td>
<td>Y</td>
<td>preterm, SGA, LBW</td>
<td>Database</td>
<td>N</td>
<td></td>
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<tr>
<td>Mod/Sev Subgroup=10264</td>
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<td></td>
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<tr>
<td>Murphy(^{8})</td>
<td>N=146</td>
<td>2005</td>
<td>Australia</td>
<td>P</td>
<td>7</td>
<td>Y</td>
<td>preterm, LBW</td>
<td>Medical records</td>
<td>Y</td>
<td></td>
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<tr>
<td>Exacerbations=52</td>
<td></td>
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<tr>
<td>Stenius-Aarniala(^{7})</td>
<td>N=504</td>
<td>1996</td>
<td>Finland</td>
<td>P</td>
<td>8</td>
<td>Y</td>
<td>preterm</td>
<td>Clinical, labor records</td>
<td>Y</td>
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<tr>
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<tr>
<td>Jana(^{13})</td>
<td>N=182</td>
<td>1995</td>
<td>India</td>
<td>P</td>
<td>8</td>
<td>Y</td>
<td>preterm, LBW</td>
<td>Clinical, case notes</td>
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<tr>
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<tr>
<td>Greenberger(^{17})</td>
<td>N=73</td>
<td>1988</td>
<td>USA</td>
<td>P</td>
<td>8</td>
<td>Y</td>
<td>preterm, LBW, SGA</td>
<td>Clinical, case notes</td>
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Exacerbations
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<tr>
<th>Subgroup=26</th>
<th>Schatz18</th>
<th>N=485</th>
<th>1995 USA</th>
<th>P</th>
<th>9</th>
<th>Y</th>
<th>Y</th>
<th>preterm, LBW, SGA</th>
<th>Clinical</th>
<th>Y</th>
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<tr>
<td></td>
<td>OCS=82</td>
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<tr>
<td></td>
<td>Exacerbations subgroup=54</td>
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<tr>
<td>Firoozi23</td>
<td>N=13007</td>
<td>2011 Canada</td>
<td>R</td>
<td>9</td>
<td>Y</td>
<td></td>
<td>preterm, LBW, SGA</td>
<td>Database</td>
<td>N</td>
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<tr>
<td></td>
<td>Mod/Sev Subgroup =2270</td>
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</tbody>
</table>

P = Prospective Study, R = Retrospective Study, OCS= Oral Corticosteroids

Table IV: Summary of studies excluded from meta-analysis

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Study and (Study Design)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Asthma Subgroup</td>
<td>Ehrenthal(R)(36), Hendler(P)(37), Fell(R)(38), Sheiner(R)(39), Acs(R)(40), Savilahti(P)(41), Beckmann(R)(42), Mihrshahi(43), Littner(R)(44), Liu(45), Demissie(R)(46), Demissie(R)(47), Wendel(RCT)(48), Lehrer(R)(49), Getahun(R)(50), Getahun(R)(51), Mabie(R)(31), Syed(R)(52), Karimi(53), Carroll(R)(54), Greenberger(55), Snyder(R)(56), Breton(R)(57), Aly(R)(58),</td>
</tr>
<tr>
<td>Subgroup Category</td>
<td>Studies</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Not Subgroup of Interest</td>
<td>Stenius-Aarniala(P)(64), Kallen(R)(65), MacMullen(R)(66), Schatz(P)(32),</td>
</tr>
<tr>
<td></td>
<td>Silverman(RCT)(67), Norjavaara(R)(68), Wen(R)(69), Minerbi-Codish(P)(70),</td>
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<td></td>
<td>Schatz(P)(16), Blais(25), Schatz(P)(71), Reece(R)(72), Dombrowski(R)(73),</td>
</tr>
<tr>
<td></td>
<td>Clark(R)(74), Alexander(R)(12), Stenius-Aarniala(P)(75), Lao(76),</td>
</tr>
<tr>
<td></td>
<td>Eltonsy(R)(77), Breton(R)(78), Moldenhauer(P)(79), Schatz(P)(80), Blais(R)</td>
</tr>
<tr>
<td></td>
<td>(81), Sarkar(P)(82), Martel(R)(83)</td>
</tr>
<tr>
<td>Inadequately Defined Subgroup</td>
<td>Triche(P)(84), Bracken(P)(10), Doucette(P)(85), Kallen(R)(86), Schatz(P)</td>
</tr>
<tr>
<td></td>
<td>(87), Bakhireva(P)(88)</td>
</tr>
<tr>
<td>No Comparison Group</td>
<td>Schatz(P)(30), Murphy(P)(29), Bakhireva(89), Namazy(P)(90),</td>
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<td>Clifton(P)(91), Olesen(R)(11), Dombrowski(92), Dombrowski(P/DBPCT)(93),</td>
</tr>
<tr>
<td></td>
<td>Bakhireva(94), Twaites(R)(95)</td>
</tr>
</tbody>
</table>

P – Prospective Study

R – Retrospective Study
Table V: Perinatal Outcomes for all Subgroups -.* p<0.05; RR= relative risk; 95% CI= 95% confidence interval

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Severity</th>
<th>Exacerbation</th>
<th>OCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>RR 1.06 95%CI[0.97,1.17]</td>
<td>RR 1.54[0.89,2.69]</td>
<td>RR 1.51,95%CI [1.15,1.98]</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>RR 1.15, 95%CI [1.05, 1.26]</td>
<td>RR 3.02[1.87,4.89]</td>
<td>RR 1.41,95%CI [1.04,1.93]</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td><strong>RR 1.16,95%CI[1.01,1.33]</strong></td>
<td>RR 0.78[0.25,2.48]</td>
<td>RR [0.81,95%CI[0.48,1.34]</td>
</tr>
</tbody>
</table>
Figure 1

Meta-analysis of cohort studies for low birth weight. "Increased Risk" indicates that the outcome was more likely in subjects with a history of asthma exacerbation during pregnancy. RR=relative risk; CI= confidence interval
<table>
<thead>
<tr>
<th>Study</th>
<th>Exacerbation n/N</th>
<th>No Exacerbation n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy</td>
<td>4/52</td>
<td>1/92</td>
</tr>
<tr>
<td>Jana</td>
<td>8/15</td>
<td>28/169</td>
</tr>
<tr>
<td>Schatz</td>
<td>4/54</td>
<td>16/432</td>
</tr>
<tr>
<td>Greenberger</td>
<td>7/26</td>
<td>5/55</td>
</tr>
</tbody>
</table>

Heterogeneity: p=0.75, I²=0%
Effect: p<0.00001

Figure 1

RR (95% CI)

Total (95% CI) 3.02 (1.87, 4.89)
Figure 2

Meta-analysis of cohort studies for preterm delivery. "Increased Risk" indicates that the outcome was more likely in subjects with a history of oral corticosteroid use during pregnancy. RR=relative risk; CI= confidence interval
Figure 2

OCS
n/N  No OCS  n/N  RR (95%CI)

Schatz\textsuperscript{20}  43/185  303/1938

Schatz\textsuperscript{17}  6/82  17/403

Total (95%CI)  1.51 (1.15, 1.98)

Heterogeneity: p=0.75, I\textsuperscript{2}=0%
Effect: p=0.003
Figure 3

Meta-analysis of cohort studies for low birth weight. "Increased Risk" indicates that the outcome was more likely in subjects with a history of oral corticosteroid use during pregnancy. RR=relative risk; CI= confidence interval
Figure 3

<table>
<thead>
<tr>
<th>OCS</th>
<th>No OCS</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td></td>
</tr>
<tr>
<td>Schatz\textsuperscript{20}</td>
<td>33/185</td>
<td>258/1938</td>
</tr>
<tr>
<td>Schatz\textsuperscript{17}</td>
<td>6/82</td>
<td>14/403</td>
</tr>
</tbody>
</table>

Heterogeneity: p=0.37, I\textsuperscript{2}=0%
Effect: p=0.03
Figure 4

Meta-analysis of cohort studies for small for gestational age. “Increased Risk” indicates that the outcome was more likely in subjects with a history of moderate to severe asthma during pregnancy. RR=relative risk; CI= confidence interval
Figure 4