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Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes

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

Cohort studies published between 1975 and March 11, 2012 were considered for inclusion. 138 publications were identified for possible inclusion, and nine papers met the inclusion criteria, by reporting perinatal outcomes of interest (low birth weight, <2500 g), pre-term 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.

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 pre-term 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.

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

KEYWORDS: Asthma, low birth weight, oral corticosteroid, pregnancy, pre-term delivery, small for gestational age

Asthma is the most common medical condition to affect pregnancy, with a prevalence of 8–13% 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 females with asthma during pregnancy are at an increased risk of perinatal complications including low birth weight, pre-term delivery and small for gestational age infants [5].

Approximately 70% of all low birth weight infants are a result of pre-term delivery before 37 completed weeks of pregnancy. Therefore, the observed increase in pre-term 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 pre-term 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 pre-term delivery [6–18]. One recent meta-analysis found that pregnant asthmatic females with a history of severe exacerbation during pregnancy are at a significantly increased risk of perinatal complications including low birth weight [19]. The use of asthma medications such as oral corticosteroids (OCS) during pregnancy may also play a potential role

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TABLE 1 Definition of ''severity'' used in studies addressing the associations between asthma severity and perinatal outcomes

First author [ref.]	Severity	Definition
Dombrowski [13]	Mild	Asthma symptoms in the previous 6 months
		Asthma symptoms <8 days in the previous 4 weeks
		FEV_1 ⩾80% pred
		Not taking daily asthma medication
	Moderate/severe	Asthma symptoms on ⩾8 days during the previous 4 weeks not attributable to a URI
		FEV_1 <60–79% pred
		Use of one or more daily medications which may include OCS in severe asthmatics
Kallen [21]	Mild	1 asthma drug
	Moderate/severe	⩾2 asthma drugs
Firoozi [22, 23]	Asthma severity index	
	Mild	ICS 0–500 $g \cdot day^{-1}$ and no additional controller therapy or 0–250 $\mu g \cdot day^{-1}$ and additional controller therapy
		No moderate-to-severe asthma exacerbation
		No more than three doses of SABA over a 12-month period
	Moderate	ICS >500 $\mu g \cdot day^{-1}$ with no additional controller therapy or doses >250 $\mu g \cdot day^{-1}$ for those receiving additional controller therapy or more than four doses SABA per week over a 12-month period and moderate-to-severe exacerbation
	Severe	ICS >1000 $\mu g \cdot day^{-1}$ or >10 doses SABA per week and moderate-to-severe exacerbation

FEV_1: forced expiratory volume in 1 s; % pred: % predicted; URI: upper respiratory infection; OCS: oral corticosteroids; ICS: inhaled corticosteroid; SABA: short-acting β-agonist.

in leading to pre-term delivery or low birth weight infants [20] and have been suggested as contributing factors by several large cohort studies [9, 13].

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 OCS use during pregnancy are associated with the risk of pre-term, low birth weight or small for gestational age infants.

METHODS

Systematic review of the literature: search strategy

English language studies published between January 1975 (when inhaled corticosteroids were introduced) and March 2012 were identified for possible inclusion from MEDLINE (n=1642), EMBASE (n=1755), Cumulative Index to Nursing and Health Literature (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 January 2009 to March 2012 to ensure that no articles were missed. The numbers for the update were: MEDLINE (n=681), EMBASE (n=624), CINAHL (n=84) and Cochrane Central Register of Controlled Trials (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, OCS use or asthma severity. Asthma was defined as physician-diagnosed asthma (whether confirmed or subject self-reported), or an asthma diagnosis as coded in a database or asthma fulfilling American Thoracic Society criteria. Females 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) [13], number of medications used to control asthma symptoms (one drug: mild; two and three drugs: moderate/severe) [21] or a validated index combining medication use and markers of exacerbation (table 1) [22, 23]. Exacerbations of asthma were defined (table 2) as symptoms requiring medical interventions such as hospitalisation, 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 OCS [7, 24]. Most studies included exacerbations occurring any time during pregnancy, with the exception of one study which limited exacerbations to the first trimester only [13]. Perinatal outcomes of interest for this article included low birth weight (<2500 g), pre-term 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. Nine papers describing seven prospective and two retrospective cohort studies met the inclusion criteria (table 3). 129 papers were excluded for the following reasons: no asthma sub-groups (n=29), poorly defined asthma sub-groups (n=6), asthma sub-groups that did not meet our inclusion criteria

TABLE 2 Definition of ''exacerbation'' used in studies addressing the associations between asthma exacerbations and perinatal outcomes

First author [ref.]	Definition of exacerbation
MURPHY [7]	Hospital admission, emergency department presentation, unscheduled doctor's visit or course of OCS
STENIUS-AARNIALA [6]	Not controlled by the patient's normal rescue medication and which was treated as an emergency (74.4% OCS)
JANA [12]	Requiring emergency services and/or hospitalisation
SCHATZ [17]	Requiring emergency therapy with nebulised bronchodilators in the clinic or emergency room
GREENBERGER [16]	Requiring adrenaline and OCS in the outpatient service, emergency room or hospital

OCS: oral corticosteroids.

(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 only (n=4), retracted article (n=1) and overlapping data with another study (n=3) (table 4).

Data extraction

Data were extracted using a standardised 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 and country of study); subject characteristics (including gestational age at recruitment, subject exclusions, maternal age, body mass index, smoking, socioeconomic status, pre-natal care, race/ethnicity and comorbidities); asthma diagnosis; severity of asthma; medication management; exacerbations; and perinatal outcome for asthma sub-groups (data mostly presented as n (%) or mean $\pm$ SD).

Study quality was assessed independently and scored by two reviewers using the Newcastle–Ottawa Scale [89]. The Newcastle–Ottawa Scale is a validated tool for assessing the quality of non-randomised studies, including cohort and case–control studies, and has a maximum score of 9. The mean quality score of included studies (8.3) (table 3) was ranked as good.

Meta-analysis

The meta-analyses conformed to standard methodological guidelines for observational studies [90]. The relative risk of the perinatal outcome was examined in sub-groups of females with asthma stratified by severity (mild *versus* moderate-to-severe), gestational asthma exacerbations (expressed as a yes/no variable) and exposure to OCS (expressed as a yes/no variable) using Review Manager software (RevMan 4.2.7, Wintertree Software Inc, Ontario, Canada). For dichotomous outcomes the relative risk (RR) and 95% confidence interval were calculated using a fixed-effects model. Heterogeneity was examined using the Chi-squared test ($p<0.1$ considered to show significant heterogeneity) and the I^2 percentage ($I^2 \geqslant 60\%$ considered to show significant heterogeneity; RevMan, Wintertree Software Inc.).

RESULTS

Relationship between asthma exacerbations and perinatal outcome

Pre-term delivery

Data on pre-term delivery was reported in five prospective studies [6, 7, 12, 16, 17] of 179 subjects experiencing exacerbations during pregnancy and 1035 subjects without exacerbations. The data from two papers from FITZSIMONS *et al.* [18] and GREENBERGER and PATTERSON [16] published in 1986 and 1988, respectively, were overlapping, and so the data from the 1988 paper, which contained a larger group of subjects, has been included here (and for subsequent analyses reported below) [16]. In the study by JANA *et al*. [12] 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 hospitalisation for symptoms. Overall, there was a nonsignificant trend of increased pre-term delivery in asthmatics with exacerbations during pregnancy (RR 1.54, 95% CI 0.89–2.69). There was no significant heterogeneity among studies ($I^2=0\%$, $p>0.1$).

Low birth weight

Data on low birth weight were included in four prospective studies [7, 12, 16, 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 in those subjects experiencing asthma exacerbation during pregnancy (RR 3.02, 95% CI 1.87–4.89). There was no significant heterogeneity among studies ($I^2=0\%$, $p>0.1$) (fig. 1).

Small for gestational age

Data on small for gestational age infants were included in two studies [16, 17] with 80 subjects experiencing exacerbations during pregnancy and 487 subjects without exacerbations. There was no significant increased risk of small for gestational age infants in those asthmatics experiencing exacerbation during pregnancy compared to those with no severe exacerbations during pregnancy (RR 0.78, 95% CI 0.25–2.48). However, significant heterogeneity was present ($I^2=71.1\%$, $p=0.06$).

TABLE 3 Summary of studies addressing effect of asthma exacerbations, oral corticosteroid (OCS) use and asthma severity on perinatal outcome

First author [ref.]	Asthma subjects (sub-groups)	Year	Region	Study design	Quality score	Severity	OCS	Exacerbations	Outcomes	Data source	Active management
Stenius-Aarniala [6]	504 (exacerbations 47)	1996	Finland	Prosp.	8			Yes	Pre-term	Clinical, labour records	Yes
Murphy [7]	146 (exacerbations 52)	2005	Australia	Prosp.	7			Yes	Pre-term, LBW	Medical records	Yes
Jana [12]	182 (exacerbations 15)	1995	India	Prosp.	8			Yes	Pre-term, LBW	Clinical, case notes	Yes
Dombrowski [13]	1739 (moderate-to-severe 866)	2004	USA	Prosp.	9	Yes			Pre-term, SGA	Clinical collection	Yes
Greenberger [16]	73 (exacerbations 26)	1988	USA	Prosp.	8			Yes	Pre-term, LBW, SGA	Clinical, case notes	Yes
Schatz [17]	485 (OCS 82, exacerbations 54)	1995	USA	Prosp.	9		Yes	Yes	Pre-term, LBW, SGA	Clinical	Yes
Schatz [20]	2123 (OCS 185)	2004	USA	Prosp.	8		Yes		Pre-term, LBW, SGA	Clinical, case notes	Yes
Kallen [21]	23 988 (moderate-to-severe 10 264)	2007	Sweden	Retro.	9	Yes			Pre-term, LBW, SGA	Database	No
Firoozi [22]	13 007 (moderate-to-severe 2270)	2011	Canada	Retro.	9	Yes			Pre-term, LBW, SGA	Database	No

Data are presented as n, unless otherwise stated. Prosp.: prospective study; LBW: low birth weight; SGA: small for gestational age; Retro.: retrospective study.

Relationship between OCS use and perinatal outcome

Pre-term delivery

Data on pre-term delivery was included in two prospective studies [17, 20] with 267 subjects who used OCS during pregnancy compared with 2341 subjects who did not use OCS during pregnancy. Overall, OCS use increased the relative risk of pre-term delivery (RR 1.51, 95% CI 1.15–1.98), with no significant heterogeneity between studies (I^2=0%, p>0.1) (fig. 2).

Low birth weight

Data on low birth weight was included in two prospective studies [17, 20] with 267 subjects who used OCS during pregnancy and 2341 subjects who did not use OCS. Overall, there was a significant increased risk of low birth weight infants to those females using OCS during pregnancy (RR 1.41, 95% CI 1.04–1.93). There was no heterogeneity between studies (fig. 3).

Small for gestational age

There were two prospective studies [17, 20] of small for gestational age, with 267 subjects who used OCS during pregnancy and 2341 subjects who did not use OCS during pregnancy. Overall, there was no significant increased risk of small for gestational age among females using OCS during pregnancy (RR 0.81, 95% CI 0.48–1.34).

Relationship between asthma severity and perinatal outcomes

Pre-term delivery

There were three studies reporting on the effect of maternal asthma severity on pre-term delivery [13, 21, 22]. One retrospective [21] and one prospective study [13] reported early pre-term delivery at <32 weeks of completed gestation as an outcome. Overall, the risk of early pre-term delivery was not increased in females with moderate-to-severe asthma compared with females with mild asthma (RR 1.08, 95% CI 0.4–1.39).

Two retrospective [21, 22] and one prospective study [13] reported pre-term delivery at <37 weeks gestation. Overall, there was no increased risk of pre-term delivery in moderate-to-severe *versus* mild asthmatic females (RR 1.00, 95% CI 0.93–1.09).

Low birth weight

Two retrospective studies [21, 22] reported low birth weight among females with mild and moderate-to-severe asthma. There was an increased risk of low birth weight in moderate-to-severe *versus* mild asthmatic females (RR 1.15, 95% CI 1.05–1.26).

Small for gestational age

There were two retrospective studies [21, 22] and one prospective study [13] with 13 400 subjects with moderate-to-severe asthma and 25 334 subjects with mild asthma severity. Meta-analysis comparing mild to moderate-to-severe asthmatics demonstrated a significantly increased risk of small for gestational age in infants of subjects with asthma classified as moderate-to-severe compared with those with mild asthma during pregnancy (RR 1.24, 95% CI 1.15–1.35). There was no significant heterogeneity between studies (I^2=20.9%, p>0.1) (fig. 4).

TABLE 4 Summary of studies excluded from meta-analysis

Reason for exclusion	Study design			
	Retrospective	Prospective	RCT	DBPCT
No asthma subgroup	Ehrenthal [25], Fell [26], Sheiner [27], Acs [28], Beckmann [29], Littner [30], Liu [31], Demissie [32, 33], Lehrer [34], Getahun [35, 36], Mabie [37], Syed [38], Karimi [39], Carroll [40], Snyder [41], Breton [42, 43], Aly [44], Almeid [45], Macmullen [46], Blais [47], Clifton [48]	Mihrshahi [49], Greenberger [50], Hendler [51], Savilahti [52]	Wendel [53]	
Not subgroup of interest	Alexander [11], Blais [24, 54], Kallen [55], Macmullen [56], Norjavaara [57], Wen [58], Reece [59], Dombrowski [60], Clark [61], Lao [62], Eltonsy [63], Breton [64], Martel [65]	Schatz [15, 66–68], Stenius-Aarniala [69, 70], Minerbi-Codish [71], Moldenhauer [72], Sarkar [73]	Silverman [74]	
Inadequately defined subgroup	Kallen [75]	Bracken [9], Triche [76], Doucette [77], Schatz [78], Bakhireva [79]		
No comparison group	Olesen [10], Twaites [80]	Bakhireva [81], Dombrowski [82], Bakhireva [83], Schatz [84], Murphy [85], Namazy [86], Clifton [87], Dombrowski [88]		Dombrowski [88]

RCT: randomised controlled trial; DBPCT: double-blind placebo controlled trial.

DISCUSSION

Previous studies, as well as a recent meta-analysis [5], have shown that pregnancies in females with asthma when compared with pregnancies in non-asthmatic females are at an increased risk of pre-term birth, low birth weight and small for gestational age infants. Until now it has been unclear which mechanisms are responsible for these observations. Our results show that exacerbations and OCS use during pregnancy are associated with an increased incidence of pre-term 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 5). These results suggest that acute asthma events (exacerbations and OCS use) increase the risk of prematurity, while greater 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 >40 000 pregnancies

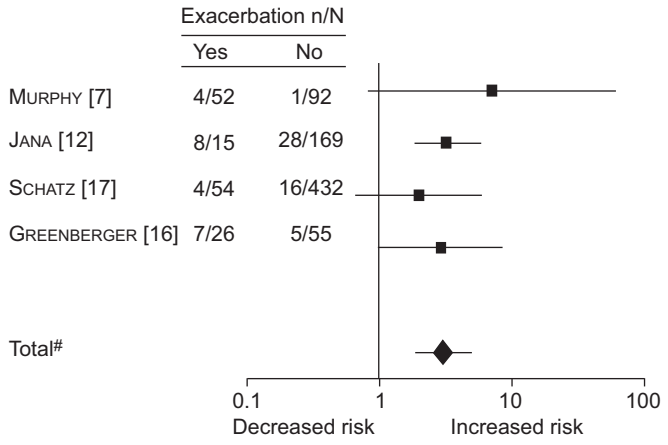

FIGURE 1. Meta-analysis of cohort studies for low birth weight. Increased risk indicates that the outcome was more likely in subjects with a history of asthma exacerbation during pregnancy. Data are presented as relative risk (95% CI). Heterogeneity: p=0.75, I^2=0%; effect: p<0.00001. #: RR 3.02 (95% CI 1.87–4.89).

found that asthmatic females with a history of exacerbation defined as acute care for asthma recorded in the databases were more likely to have a low birth weight or pre-term infant than non-asthmatic females [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 females with exacerbations compared with non-asthmatic females. This finding is at variance with our results, but may be related to the different comparison groups used in their study (non-asthmatic females) *versus* our meta-analysis (asthmatic females without exacerbations).

Another recent study of >9000 pregnant asthmatic females showed that those females with a hospitalisation or emergency department visit had an increased risk of low birth weight infants [91]. Murphy *et al*. [19] reported in a meta-analysis of 855 asthmatics that there was an increased risk of low birth weight infants but not pre-term delivery associated with

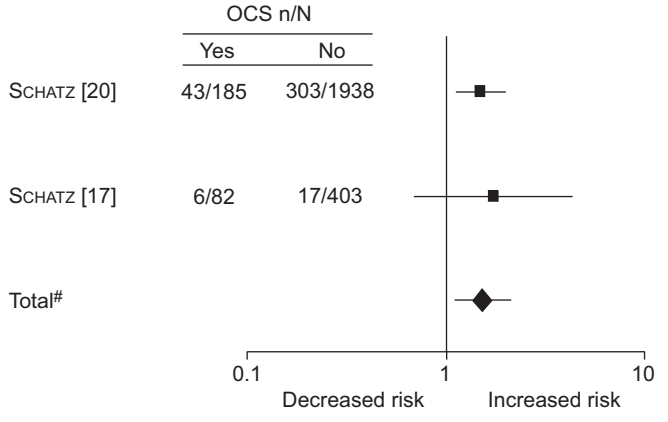

FIGURE 2. Meta-analysis of cohort studies for pre-term delivery. Increased risk indicates that the outcome was more likely in subjects with a history of oral corticosteroid (OCS) use during pregnancy. Data are presented as relative risk (95% CI). Heterogeneity: p=0.75, I^2=0%; effect: p=0.003. #: RR 1.51 (95% CI 1.15–1.98).

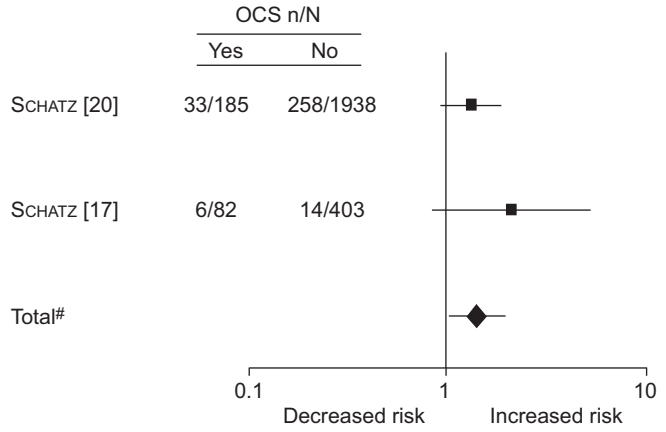

FIGURE 3. Meta-analysis of cohort studies for low birth weight. Increased risk indicates that the outcome was more likely in subjects with a history of oral corticosteroid (OCS) use during pregnancy. Data are presented as relative risk (95% CI). Heterogeneity: p=0.37, I^2=0%; effect: p=0.003. #: RR 1.41 (95% CI 1.04–1.93).

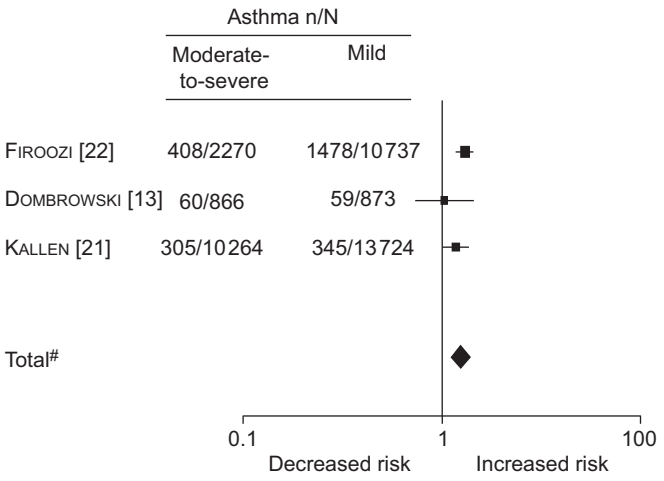

FIGURE 4. Meta-analysis of cohort studies for small for gestational age infants. Increased risk indicates that the outcome was more likely in subjects with a history of moderate-to-severe asthma during pregnancy. Data are presented as relative risk (95% CI). Heterogeneity: p=0.28, I^2=20.9%; effect: p=0.00001. #: RR 1.24 (95% CI 1.15–1.35).

exacerbations during pregnancy. For our meta-analysis, the cause of asthma exacerbations was unknown in all studies except one [7], whose authors found that triggers included non-adherence to inhaled corticosteroid medications in about a third of patients and viral infection in another third. STENIUS-AARNIALA *et al*. [6] found that 31 out of the 45 subjects with a history of exacerbation during pregnancy were not using inhaled corticosteroids. 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 females who had a severe exacerbation and those who did not [7, 17]. An interesting observation by GREENBERGER and PATTERSON [16] was that while subjects with untreated status asthmaticus had a higher risk of adverse perinatal outcomes, those subjects who were treated for exacerbations with inhaled corticosteroids or OCS had much more favourable outcomes. In our analysis, the relative risk of low birth weight in OCS users (RR 1.41) was approximately half that of females 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 [85], both of which could presumably be mitigated by prevention or possibly expeditious treatment of asthma exacerbations.

When we examined the potential effect of OCS use on perinatal outcomes, we found that pregnant asthmatic females who used OCS during pregnancy had an increased risk of pre-term 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 pre-term delivery that may be related to OCS use. Pregnant asthmatics taking a mean daily dose of 8 mg of prednisone a day had an increased risk of pre-term delivery [80]. DOMBROWSKI *et al*. [13] found a significant effect of severe asthma (forced expiratory volume in 1 s (FEV_1) <60% and/or OCS use in the 4 weeks prior to enrolment) on pre-term delivery with an adjusted odds ratio of 2.2 (95% CI 1.2–4.2). BRACKEN *et al*. [9] studied 873 pregnant females with a history of asthma (of whom 778 had no physician diagnosis, only asthma symptoms) and showed increased odds of pre-term delivery with the use of OCS (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*. [14] compared 31 steroid-dependent asthmatics to 50 non-steroid-dependent asthmatics and found a significantly increased risk of pre-term delivery and low birth weight in the group dependent on OCS.

Since OCS are most commonly used over a short-term to treat exacerbations (which the present 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

TABLE 5 Perinatal outcomes for all sub-groups

Outcome	Severity	Exacerbation	OCS
Pre-term delivery	1.06 (0. 97–1.17)	1.54 (0.89–2.69)	1.51 (1.15–1.98)*
Low birth weight	1.15 (1.05–1.26)*	3.02 (1.87–4.89)*	1.41 (1.04–1.93)*
Small for gestational age	1.16 (1.01–1.33)*	0.78 (0.25–2.48)	0.81 (0.48–1.34)

Data are presented as relative risk (95% CI). OCS: oral corticosteroids. *: p<0.05.

OCS may be related to their being a marker for asthma exacerbations. One study did report an association of OCS with prematurity after adjusting for exacerbations and FEV1. Thus a direct effect of OCS 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 OCS, 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 β-agonists, inhaled corticosteroids or theophylline contribute to the increased risk of pre-term delivery, low birth weight or small for gestational age in the pregnancies of asthmatic females. 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 females with lower FEV1 or severe asthma have an increased risk of adverse perinatal outcomes [40] which include small for gestational age infants [15, 57, 92]. DOMBROWSKI *et al*. [13] adjusted for potential confounders such as smoking, race and socioeconomic status and found that there remained an increased risk of small for gestational age in moderate-to-severe asthmatics. We were unable to separate which of the moderate-to-severe asthmatics had sub-optimally 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 [93].

It can be hypothesised 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 pre-term labour and pre-term delivery [5]. This observation may be explained by active asthma management reducing exacerbations, or courses of OCS, both of which have been implicated in some studies as contributing to the risk of pre-term delivery [19].

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 females with moderate-to-severe asthma or exacerbations of asthma during pregnancy were at a higher risk of having a premature, low birth weight 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 and 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 minimising symptoms, exacerbations, limitations in activities and need for rescue medications [94].

In conclusion, the current meta-analysis indicates that those pregnant asthmatics with asthma exacerbations, need for OCS and moderate-to-severe asthma are at an increased risk of pre-term delivery, low birth weight and small for gestational age infants. 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.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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