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Murphy, V. E.; Wang, G.; Namazy, J. A.; Powell, H.; Gibson, P. G.; Chambers, C.; Schatz, M. "The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis" BJOG: An International Journal of Obstetrics and Gynaecology Vol. 120, Issue 7, p. 812-822 (2013)

Available from: <http://dx.doi.org/10.1111/1471-0528.12224>

Accessed from: <http://hdl.handle.net/1959.13/1052125>

The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis.

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Running Title:

Maternal asthma and neonatal outcomes: meta-analysis

Word Count: 4005

Abstract

Background: There is conflicting literature on the effect of maternal asthma on congenital malformations and neonatal outcomes.

Objectives: This review and meta-analysis sought to determine if maternal asthma is associated with an increased risk of adverse neonatal outcomes.

Search Strategy: We searched electronic databases for: (asthma or wheeze) and (pregnan* or perinat* or obstet*).

Selection Criteria: Cohort studies published between 1975 and March 2012 reporting at least one perinatal outcome of interest (congenital malformations, neonatal complications, perinatal mortality).

Data Collection and Analysis:

21 studies met inclusion criteria in pregnant women with and without asthma. Further analysis was conducted on 16 studies where asthmatic women were stratified by exacerbation history, corticosteroid use, bronchodilator use or asthma severity.

Main Results: Maternal asthma was associated with a significantly increased risk of congenital malformations (RR 1.11, 95% CI [1.02, 1.21], $I^2=59.5\%$), cleft lip with or without cleft palate (RR 1.30, 95% CI [1.01, 1.68], $I^2=65.6\%$), neonatal death (RR 1.49, 95% CI [1.11, 2.00], $I^2=0\%$), and neonatal hospitalisation (RR 1.50, 95% CI [1.03, 2.20], $I^2=64.5\%$). There was no significant effect of asthma on major malformations (RR 1.31, 95% CI [0.57, 3.02], $I^2=70.9\%$) or stillbirth (RR 1.06, 95% CI [0.9, 1.25], $I^2=35\%$).

Exacerbations, bronchodilator and ICS use were not associated with congenital malformation risk.

Conclusions: Despite limitations related to the observational nature of the primary studies, this review demonstrates a small increased risk of neonatal complications among pregnant women with asthma. Further investigations into mechanisms and potential preventative interventions to improve infant outcomes are required.

Key Words: asthma, pregnancy, congenital anomaly, malformation, perinatal mortality, stillbirth, neonatal death, NICU

Abstract word count: 249

Introduction

Asthma is a commonly reported medical condition affecting pregnant women, and the course of the disease can change during pregnancy. There has been conflicting literature as to the effects of maternal asthma on pregnancy and neonatal outcomes. In 2011, we published the first systematic review and meta-analysis of literature in this area examining the risk of adverse perinatal outcomes in women with asthma, focusing on preterm delivery, low birth weight and pre-eclampsia, some of the more commonly reported outcomes ¹. We found a moderately increased risk of each of these outcomes in pregnant women with asthma compared to pregnant women without asthma ¹. Numerous other important adverse outcomes, particularly those affecting the neonate, have been reported in the literature, but with no previous attempt to summarise the data via meta-analysis. Studies on the effect of asthma on congenital malformations vary in terms of sample size, study design (cohort vs case control), exposures tested (asthma or asthma medication use), adjustment for confounders and multiple testing, and examination of specific malformations, while studies of perinatal mortality have generally been underpowered. There are also few studies which examine the potential mechanisms contributing to these outcomes, such as disease severity, exacerbations or asthma medication use. This updated systematic review and meta-analysis attempts to overcome some of these limitations in the existing literature, by examining the relative risks of adverse neonatal outcomes among women with asthma compared to women without asthma, and to examine the possible roles of medication use, asthma exacerbations during pregnancy and asthma severity on these outcomes.

Methods

Search Strategy and Study Selection

A review protocol was established by the investigators prior to commencement. The study protocol has been described in detail elsewhere ¹ and further details are given in the online supporting information. We recently completed an update to our original systematic review. The initial search

identified English language studies published between 1975 (when inhaled corticosteroids were introduced) and March 2009 from Medline (n=1642), Embase (n=1755), CINAHL (n=417), and the Cochrane Central Register of Controlled Trials (n=75), using the search terms ((asthma or wheeze) and (pregnan* or perinat* or obstet*)). 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. In the update, we used the same search terms to identify English language studies published between January 2009 and March 11, 2012 from Medline (n=681), Embase (n=624), CINAHL (n=84) and the Cochrane Central Register of Controlled Trials (n=14).

Inclusion criteria for analysis of the effect of maternal asthma on neonatal outcomes (Analysis A)

Included articles contained data from a group of pregnant women with asthma and a control group of pregnant women without asthma. Further inclusion criteria were 1) reporting at least one perinatal outcome of interest (congenital malformation, major congenital malformation, perinatal mortality, stillbirth, neonatal death, neonatal hospitalisation, transient tachypnea of the newborn, respiratory distress syndrome or neonatal sepsis) and 2) cohort study design (prospective or retrospective). Maternal asthma could be defined as physician diagnosed (whether confirmed or subject self-report), database-coded asthma diagnosis, or asthma fulfilling American Thoracic Society criteria.

139 articles were identified for possible inclusion in the review (Analysis A). 73 of these were excluded for the following reasons: no control group (n=38), no clear asthma group (n=3), asthma subjects selected based on exacerbation (n=3), cross sectional survey (n=3), case-control study (n=3), perinatal outcomes not suitably reported (n=10), subjects studied prior to 1975 (n=2), paper retracted (n=1), abstract only (n=2), not the primary paper/first report of results (n=2), review (n=6).

Of the remaining 66 publications, 21 studies (8 prospective, 13 retrospective) were identified for inclusion in the analysis of the effect of maternal asthma on neonatal outcomes (Table S1).

Inclusion criteria for analysis of the effect of maternal asthma subtypes on neonatal outcomes (Analysis B)

Included articles contained data from pregnant women with asthma which had been sub-divided based on asthma medication use (eg ICS use, no ICS use), asthma exacerbations requiring medical intervention during pregnancy, or asthma severity (mild, moderate/severe, Table S2). Cohort studies or randomised controlled trials were included if they reported at least one outcome of interest.

Of the studies identified for Analysis A, and the 38 studies which were excluded from Analysis A because they contained no control group, there were 16 studies (7 prospective, 8 retrospective, 1 randomised controlled trial) identified for inclusion in the analysis of the effect of maternal asthma subtypes on neonatal outcomes (Analysis B).

Data extraction

Data extraction was completed on a standardised form by one reviewer and checked by a second reviewer. Investigators discussed any discrepancies to reach consensus. Studies were considered to have provided active asthma management when the study investigators were involved in the management and treatment of subjects with asthma and this was described (Table S1).

We used the Newcastle-Ottawa Scale (NOS) to assess study quality². 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. Quality was assessed and scored by two reviewers and all studies were considered to be of adequate quality for inclusion in the meta-analysis (minimum score 5, mean of all scores 7.8, Table S1).

Meta-Analysis

The meta-analyses conformed to standard methodological guidelines for meta-analysis of observational studies ³. The relative risk of the perinatal outcome was examined in women with asthma compared to women without asthma (analysis A) or in subgroups of women with asthma stratified by severity (mild versus moderate-severe), exacerbations during pregnancy (expressed as a yes/no variable) and exposure to oral corticosteroids during pregnancy (expressed as a yes/no variable, analysis B) 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>). Sensitivity analyses were also performed in Analysis A by study design (prospective vs retrospective cohort) and asthma management (active vs no active management). For dichotomous outcomes the relative risk with 95% confidence interval was calculated using a random effects model, unless 3 or fewer studies were combined, in which case the fixed effects model was used. The difference between relative risks for the active management and no active management subgroups was determined using the method of Altman and Bland ⁴ and expressed as a relative risk ratio (RRR) with 95% confidence intervals. Data from studies which provided adjusted odds ratios were pooled using the generic inverse variance method. Heterogeneity was examined using the Chi-squared test ($P < 0.1$ considered significant heterogeneity), the I-square percentage ($I^2 \geq 60\%$ considered significant heterogeneity) and subgroup analyses.

Other Analyses

When outcomes were reported in at least 10 studies, Funnel plots and the Egger test were used to investigate publication bias (Stata 7, Stata Corporation, www.stata.com). Power calculations were conducted using the PS Power and Sample size Program (version 2.1.30) ⁵. In reporting results of the meta-analysis we followed recommendations from the PRISMA consensus statement ⁶.

Further information is available in Appendix 1: Supplementary methods.

Results

Congenital malformations

Data on congenital malformations (all/any) was included in 16 publications⁷⁻²² which represented 14 overall studies. Data from Minerbi-Codish et al.¹⁴ was incomplete and therefore not included in the meta-analysis. Schatz et al reported major and minor congenital malformations separately, which were added together to give total malformations¹⁸. Clark et al. reported malformations as those which were the reason for neonatal hospital admissions, so this data was excluded as it did not capture all malformations⁸. Data sources and definitions/confirmation of congenital malformations and major congenital malformations varied (Table S3).

There were four prospective cohort studies (all had active asthma management) included in the meta-analysis and 8 retrospective cohort studies (none had active management)^{7 9 10 12 13 20-22}. There was a significantly increased risk of congenital malformations in women with asthma compared to control women without asthma (Figure 1A, RR 1.11, 95% CI [1.02, 1.21], $I^2 = 59.5\%$, $P < 0.1$). Sensitivity analysis showed the effect was only significant in the sub-category of retrospective cohort studies (without active management, RR 1.12 (95% CI [1.03, 1.22]), while in the prospective cohort studies (with active asthma management) there was no significant effect (RR 1.40, 95% CI [0.54, 3.59]). However, the prospective cohort studies only had 10% power to detect a RR of 1.11, as observed in the retrospective studies. There was no significant publication bias (Eggers test, $P = 0.977$).

A meta-analysis of the adjusted odds ratio (OR) from four studies (retrospective, no active management)^{9 12 13 22} found an increased odds of congenital malformations among women with asthma (Figure 1B, OR 1.18, 95% CI [1.03, 1.35]).

The relative risk of congenital malformations of among subgroups of women with asthma (Table 2) indicated no increased risk of malformations with bronchodilator use²³⁻²⁵, ICS use^{9 26 27} or exacerbations^{16 17 25} (Table 1).

Four prospective studies reported major congenital malformations^{18 28-30}. The meta-analysis indicated no significant risk of maternal asthma (Table 1, RR 1.31, 95% CI [0.57, 3.02]), however, there was significant heterogeneity between studies ($I^2 = 70.9\%$, $P < 0.1$). The study from Bakhireva et al. reported an unusually low prevalence of major malformations in the control group, which contributed to the vastly different result from this study²⁸.

There was no significantly increased risk of major malformations with bronchodilator use when data from two studies^{31 32} was combined (Table 1, RR 1.00, 95% CI [0.80, 1.26]). Data on major congenital malformations among women with and without asthma exacerbations was extracted from four publications^{25 32-34}. However, there was significant similarity in the cohorts from the Canadian studies^{25 32 34} and data were included in the meta-analysis from Eltonsy et al., 2011²⁵ only, as this covered the longest time period (1990-2002) and the largest number of asthmatic pregnancies (13117 compared to 4344 in Blais et al, 2008³⁴ and 4561 in Blais et al, 2007³²). There was no significantly increased risk of major malformations among women with asthma exacerbations during pregnancy compared to women with no exacerbations during pregnancy (Table 1, RR 1.26, 95% CI [0.95, 1.67]), with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.71$).

Specific congenital malformations were described in detail by Kallen et al.⁹ and Blais et al.²². Kallen et al. found a significant increase in cardiac defects and anal atresia among women with asthma compared to population estimates⁹. Blais et al found that women with asthma were at increased risk of nervous system, respiratory system and digestive system defects²². We combined data on cleft lip and/or cleft palate which was described in both papers, demonstrating that infants from women with asthma had a significantly increased risk of this malformation compared to infants from women without asthma (Table 1, RR 1.30, 95% CI [1.01, 1.68], $I^2=65.6\%$).

Stillbirth

Data on stillbirth (fetal death *in utero* either >20 weeks, or >500 g or >28 weeks³⁵) were included in 8 studies^{13 15 18 21 24 35-37}. Two publications from Stenius-Aarniala et al. contained the same population of subjects^{15 16}, but had inconsistencies in the description of perinatal deaths. The first publication contained a detailed description of all perinatal deaths (including separate data on stillbirths and neonatal deaths); therefore data from the original paper was included in this analysis¹⁵. Overall, there was no significantly increased risk of stillbirth in infants of asthmatic mothers compared to control mothers (Figure 2A, RR 1.06, 95% CI [0.90, 1.25]), and there was no heterogeneity in the studies ($I^2 = 35\%$, $P>0.1$). There was also no increased risk in the sub-analyses by study design (Figure 2A), asthma management (data not shown), or adjusted odds ratio (Table 2).

There were no significant associations between exacerbations^{33 38} or ICS use^{39 40} and the risk of stillbirth among women with asthma (Table 2).

Neonatal Death

Data on neonatal death (death up to one month of age) were included in six studies, two prospective cohort studies^{15 18} and four retrospective cohort studies^{8 24 37 41}. Overall, there was a significantly

increased risk of neonatal death in infants of asthmatic mothers compared to control mothers (Figure 2B, RR 1.49, 95% CI [1.11, 2.00], no heterogeneity, $I^2=0\%$, $P=0.67$). Individually, only the retrospective cohort sub-category showed a statistically increased risk which was of similar magnitude to the overall effect size (RR 1.48, 95% CI [1.10, 1.99]).

In three studies, subjects had active management of their asthma by the study investigators or local hospital^{15 18 24}, while in three studies no active management of subjects was given^{8 37 41}. In the sub-category with active management, there was no significant effect of maternal asthma on neonatal death, but the confidence interval was very wide (RR 2.28, 95% CI [0.46, 11.40]). These studies were underpowered (6%) to detect the difference observed in the retrospective cohort studies. In the sub-category of studies with no active management of subjects, there was a significant effect of maternal asthma on neonatal death (RR 1.47, 95% CI [1.09, 1.98]). The difference between the relative risks of the no active management and active management sub-groups was not significant (ratio of relative risk (RRR) 1.55, 95% CI [0.30, 7.94], $P=0.598$).

Perinatal Mortality

Data on perinatal mortality (a combination of stillbirths and neonatal deaths) was included in 9 studies from 10 publications. There were overlapping data presented in two publications from Schatz et al.^{18 19}. Only the more recent paper with larger numbers and more definitively matched subjects was included in the analysis¹⁸.

There were six prospective cohort studies^{11 15 17 18 29 42} and three retrospective cohort studies^{10 24 37}. Overall, there was a significantly increased risk of perinatal mortality in infants of asthmatic mothers compared to control mothers (Figure 2C, RR 1.25, 95% CI [1.05, 1.50], $I^2=0\%$), with the overall effect size being intermediate between that observed for stillbirth and neonatal death. Individually, neither the prospective or retrospective cohort sub-categories showed a statistically

increased risk of perinatal mortality (Figure 2C). The prospective cohort studies were underpowered to detect a RR of 1.25 (11%).

There were seven studies where subjects had active management of their asthma^{11 15 17 18 24 29 42} and two studies where no active management was given^{10 37}. There was no significant heterogeneity between studies, and in neither sub-category was the risk of perinatal mortality significantly increased in women with asthma compared to control women, although the effect sizes were similar to the overall result (active management: RR 1.17, 95% CI [0.61, 2.27], no active management RR 1.23, 95% CI [0.95, 1.58]). The active management studies were underpowered to detect a RR of 1.23 (11%).

Women with exacerbations were not at significantly increased risk of perinatal mortality compared to women without exacerbations^{16 17 33} (Table 2). Women with moderate/severe asthma were not at significantly increased risk of perinatal mortality compared to women with mild asthma^{29 35 42} (Table 2).

Neonatal hospitalisation

Data on neonatal hospitalisation (treatment in or admission to the neonatal intensive care unit, or neonatal medical/surgical unit) were included in 6 publications. There were four prospective cohort studies^{16 29 42 43} and two retrospective cohort studies^{8 20}. Overall, there was a significantly increased risk of neonatal hospitalisation among infants of asthmatic mothers (Figure 3, RR 1.50, 95% CI [1.03, 2.20]) compared to infants of mothers without asthma. There was significant heterogeneity between studies ($I^2=64.5\%$, $P=0.02$), and the risk was significant in the retrospective cohort sub-category only (RR 2.36, 95% CI [1.10, 5.04]). Three studies had active management^{15 29 42}, while three did not^{8 20 43}. There was a significant risk of neonatal hospitalisation among studies with no active management (RR 1.97, 95% CI [1.07, 3.65]), but not among studies with active management

(RR 1.13, 95% CI [0.95, 1.36]). The difference between the relative risks of the no active management and active management sub-groups was not significant (RRR 0.57, 95% CI [0.30, 1.09], P=0.088).

Two of the studies excluded both asthmatic and control women with earlier deliveries (one excluded subjects who were less than 36 weeks at recruitment⁴³, while another excluded all preterm deliveries⁸), which may result in fewer neonatal complications than other studies. When sensitivity analysis was conducted without these 2 studies, the risk of neonatal hospitalisation among women with asthma was of a similar effect size (RR 1.58, 95% CI [0.84, 2.99]), but was not significant.

Transient Tachypnea of the Newborn (TTN)

TTN was evaluated in three studies^{8 29 44}. TTN data was reported twice in publications from Schatz et al.^{19 44}, and the data from the publication specifically on TTN was used⁴⁴. Two prospective cohort studies (both with active management) were included in the meta-analysis and there was a significantly increased risk of TTN among infants of asthmatic mothers (Table 2, RR 1.54, 95% CI [1.09, 2.18]) compared to infants of mothers without asthma and significant heterogeneity between studies ($I^2=84.3\%$, $P=0.002$). The retrospective study from Clark et al.⁸ included more severe cases of TTN requiring hospitalisation, and was the only study to individually report a significantly increased risk of TTN in neonates of mothers with asthma compared to mothers without asthma (RR 6.32, 95% CI [1.88, 21.28]). We included this study in the meta-analysis because it was not clear whether the TTN diagnosis required hospitalisation in the other studies, and since the criteria for the diagnosis of TTN in asthma and control subjects would be the same in each study, we expected the relative relationships between pregnancies in asthmatic versus control women to hold across studies.

Respiratory Distress Syndrome (RDS)

Data on infant RDS (also called hyaline membrane disease) was included in two studies, which were both prospective cohort studies with active asthma management ^{18 29}. The meta-analysis did not identify an increased risk of RDS among infants of asthmatic mothers (Table 2, RR 1.57, 95% CI [0.88, 2.81]).

Neonatal Sepsis

Neonatal sepsis was defined as a discharge diagnosis of neonatal sepsis ²⁹, or sepsis resulting in admission to the neonatal medical or surgical unit ⁸, and there was a significantly increased risk of sepsis among infants of asthmatic mothers (Table 2, RR 2.27, 95% CI [1.12, 4.58]) compared to infants of mothers without asthma.

Discussion

Main Findings

This meta-analysis indicates that infants of pregnant women with asthma are 11% more likely to manifest congenital malformations compared to infants of non-asthmatic women. Significance was reached in the retrospective studies, and among 4 studies which controlled for important confounders and reported adjusted OR data. . It is likely that some studies reported major malformations only (those that were recognised at birth), however a separate analysis of studies reporting major malformations showed no increased risk with maternal asthma. One possibility is that the risk of malformations is driven by minor malformations, which would be reassuring, since these are less clinically significant. However, the analysis of major malformations may be inadequately powered, since there were fewer studies and subjects reporting this outcome. More data are needed to clarify these risks.

Pregnant women with asthma were at 30% increased risk of cleft lip and/or palate compared to pregnant women without asthma. Previous case-control studies demonstrated an association

between first trimester oral corticosteroid exposure and the risk of oral clefts^{45 46}. Our finding is consistent with the possibility that only those women with asthma who used oral steroids in the critical window for lip and palate closure are at risk for these specific defects.

Several cohort studies have specifically examined the effects of corticosteroid treatment on malformations. Two studies, exclusively in women using budesonide, found no increased risk of malformations^{26 50}. Kallen et al. evaluated the risk of malformations in women using oral or inhaled corticosteroids in early pregnancy, but found no significant associations⁹. Another large study found a significantly reduced risk of malformations among first trimester users of moderate dose ICS compared to non-users³². There was no increased risk with the use of high dose ICS, however, women who experienced exacerbations requiring medical intervention in the first trimester were at significantly increased risk of congenital malformations compared to women without exacerbations³⁴. Our meta-analysis combined this data³⁴ with that from two other studies and no increased risk with exacerbation was observed.

There was a 25% increased risk of perinatal mortality in women with asthma, which was likely driven by the increase in neonatal deaths. However, this risk is small compared to risks for IVF pregnancies (OR 2.2, 95% CI [1.6, 3.0])⁵³ or diabetic pregnancies (RR 3.01, 95% CI [1.55, 5.84])⁵⁴. The increase in neonatal mortality may be a result of the increased risk of preterm deliveries¹, since the increased risk of perinatal mortality reported by one study was eliminated when adjusted for prematurity³⁷.

Subgroup analyses did not confirm a relationship between asthma management or severity and adverse neonatal outcomes. However, the primary studies were limited in their ability to define asthma control and successful management in individual women. A recent RCT demonstrated that neonatal outcomes could be modified when asthma therapy was adjusted according to the degree of

airway inflammation, rather than symptoms and lung function⁵⁷. This management strategy halved the rate of exacerbations requiring medical intervention during pregnancy, suggesting the potential to improve maternal and neonatal health through active management. Large prospective studies with comprehensive assessment of individual patient control and treatment variables as well as relevant confounders may further support the hypothesis that optimal asthma control during pregnancy mitigates the increased perinatal risks demonstrated in asthmatic pregnancies.

Strengths and Weaknesses

In this systematic review and meta-analysis, we have identified numerous risks, which, although small in size, are consistent and significant. The major strength of this approach is the large number of pregnancies studied and the large number of rare events reported. There are limitations arising from the observational nature of the included studies, such as risk of bias (including reporting bias), the influence of confounders and the presence of significant heterogeneity in some analyses. For congenital malformations, we were able to combine data which adjusted for confounders and found a similar result as when combining unadjusted data, suggesting a minimal effect of confounders. Significant heterogeneity was present in several of the analyses. However, analyses for stillbirth, neonatal death and perinatal mortality and asthma subgroup analyses for congenital malformations were not affected by heterogeneity. It is possible that the very large sample sizes in some of the retrospective studies result in heterogeneity which is overstated compared to traditional meta-analyses.

Interpretation

It is plausible that maternal asthma may contribute to adverse neonatal outcomes since women with asthma are at increased risk of low birth weight¹, preterm delivery¹, gestational diabetes and placental problems⁵⁸ which all increase the risk of neonatal complications and death. Using data from different populations and settings, with varying study designs, results indicate that neonates of

women with asthma are at a small risk of serious complications including intensive care hospitalisation. While we did not observe associations between asthma severity or exacerbations and neonatal outcomes, the number of available studies was low. There was a small but inconsistent effect of asthma on congenital malformations and further research is needed to clarify the risk of this outcome, and whether the risks found here could be driven by minor malformations.

Conclusions

Asthma is a common chronic disease among pregnant women, and the risks of adverse outcomes for both mother and baby during the perinatal period make this a significant health issue. Pregnant women with asthma are at increased risk of any congenital malformation and specifically of cleft lip and/or cleft palate. The currently available evidence does not indicate any relationship between malformations and bronchodilator use, ICS use or exacerbations. Neonates were also at increased risk of intensive care hospitalisation and death, although further studies are needed to elucidate the mechanisms involved. Results should be interpreted with caution due to the small absolute risks for women with this prevalent condition. Pending additional data, early pregnancy care to achieve good asthma control and avoid exacerbations seems warranted, which should improve maternal and neonatal health.

Acknowledgements

The authors thank Prof John Attia for his advice on the meta-analyses and Dr Patrick McElduff for statistical advice.

Disclosure of Interests

Potential Conflicts of Interest:

Vanessa E Murphy: None

Wang Gang: None

Jennifer A. Namazy: Genentech

Heather Powell: None

Peter G Gibson: Glaxo Smith Kline, Boehringer Ingelheim

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

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

Contribution to Authorship

VM: conception, study search and identification, inclusion/exclusion, data extraction, quality assessment, interpretation and writing.

WG: study search and identification, inclusion/exclusion, data extraction, quality assessment, manuscript editing.

JN: study search and identification, inclusion/exclusion, data extraction, quality assessment, interpretation and manuscript editing.

HP: study search and identification, inclusion/exclusion, data extraction, quality assessment, analysis and manuscript editing.

PG: study design and conception, interpretation, writing and manuscript editing

CC: interpretation and manuscript editing

MS: study design and conception, interpretation, writing and manuscript editing.

Details of Ethics Approval

Not applicable

Funding

Kaiser Permanente Southern California Regional Research Committee.

The funding body played no role in the conduct or reporting of this research.

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Table and Figure Caption List

Table 1: Congenital malformations and related outcomes in pregnant women with asthma

Table 2: Neonatal outcomes in pregnant women with asthma

Figure 1: (A) Meta-analysis of cohort studies for congenital malformations. “Increased risk” indicates that the outcome was more likely to subjects with asthma. (B) Meta-analysis of cohort studies which adjusted for confounders and presented data as OR for congenital malformations. “Increased odds” indicates that the outcome was more likely to subjects with asthma.

RR: relative risk, CI: confidence interval, OR: odds ratio.

Figure 2: (A) Meta-analysis of cohort studies for stillbirth. (B) Meta-analysis of cohort studies for neonatal death. (C) Meta-analysis of cohort studies for perinatal mortality. “Increased risk” indicates that the outcome was more likely in subjects with asthma. RR: relative risk, CI: confidence interval.

Figure 3: Meta-analysis of cohort studies for neonatal hospitalisation. “Increased risk” indicates that the outcome was more likely in subjects with asthma. RR: relative risk. CI: confidence interval.