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Interventions for managing asthma in pregnancy (Review)

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[Intervention Review]

Interventions for managing asthma in pregnancy

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ABSTRACT

Background

Asthma is the most common respiratory disorder complicating pregnancy, and is associated with a range of adverse maternal and perinatal outcomes. There is strong evidence however, that the adequate control of asthma can improve health outcomes for mothers and their babies. Despite known risks of poorly controlled asthma during pregnancy, a large proportion of women have sub-optimal asthma control, due to concerns surrounding risks of pharmacological agents, and uncertainties regarding the effectiveness and safety of different management strategies.

Objectives

To assess the effects of interventions (pharmacologic and non-pharmacologic) for managing women's asthma in pregnancy on maternal and fetal/infant outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (2 June 2014) and the Cochrane Airways Group's Trials Register (4 June 2014).

Selection criteria

Randomised and quasi-randomised controlled trials comparing any intervention used to manage asthma in pregnancy, with placebo, no intervention, or an alternative intervention. We included pharmacological and non-pharmacological interventions (including combined interventions). Cluster-randomised trials were eligible for inclusion (but none were identified). Cross-over trials were not eligible for inclusion.

We included multi-armed trials along with two-armed trials. We also included studies published as abstracts only.

Data collection and analysis

At least two review authors independently assessed trial eligibility and quality and extracted data. Data were checked for accuracy.

Main results

We included eight trials in this review, involving 1181 women and their babies. Overall we judged two trials to be at low risk of bias, two to be of unclear risk of bias, and four to be at moderate risk of bias.

Five trials assessed pharmacological agents, including inhaled corticosteroids (beclomethasone or budesonide), inhaled magnesium sulphate, intravenous theophylline, and inhaled beclomethasone verus oral theophylline. Three trials assessed non-pharmacological interventions, including a fractional exhaled nitric oxide (FENO)-based algorithm versus a clinical guideline-based algorithm to adjust inhaled corticosteroid therapy, a pharmacist-led multi-disciplinary approach to management versus standard care, and progressive muscle relaxation (PMR) versus sham training.

The eight included trials were assessed under seven separate comparisons.

Pharmacological interventions

Primary outcomes: one trial suggested that inhaled magnesium sulphate in addition to usual treatment could reduce exacerbation frequency in acute asthma (mean difference (MD) -2.80; 95% confidence interval (CI) -3.21 to -2.39; 60 women). One trial assessing the addition of intravenous theophylline to standard care in acute asthma did not report on exacerbations (65 women). No clear difference was shown in the risk of exacerbations with the use of inhaled beclomethasone in addition to usual treatment for maintenance therapy in one trial (risk ratio (RR) 0.36; 95% CI 0.13 to 1.05; 60 women); a second trial also showed no difference, however data were not clearly reported to allow inclusion in a meta-analysis. No difference was shown when inhaled beclomethasone was compared with oral theophylline for maintenance therapy (RR 0.88; 95% CI 0.59 to 1.33; one trial, 385 women). None of these trials reported on neonatal intensive care admissions.

Secondary outcomes: inhaled magnesium sulphate in acute asthma was shown to improve lung function measures (one trial, 60 women); intravenous theophylline in acute asthma was not associated with benefits (one trial, 65 women). No clear differences were seen with the addition of inhaled corticosteroids to routine treatment in three trials (374 women). While inhaled beclomethasone, compared with oral theophylline, significantly reduced treatment discontinuation due to adverse effects in one trial (384 women), no other differences were observed, except for higher treatment adherence with theophylline. Four of the five trials did not report on adverse effects.

Non-pharmacological interventions

Primary outcomes: in one trial, the use of a FENO-based algorithm was shown to significantly reduce asthma exacerbations (RR 0.61; 95% CI 0.41 to 0.90; 220 women); and a trend towards fewer neonatal hospitalisations was observed (RR 0.46; 95% CI 0.21 to 1.02; 214 infants). No exacerbations occurred in one trial assessing pharmacist-led management; this approach did not reduce neonatal intensive care admissions (RR 1.50; 95% CI 0.27 to 8.32; 58 infants). One trial (64 women) assessing PMR did not report on exacerbations or neonatal intensive care admissions.

Secondary outcomes: the use of a FENO-based algorithm to adjust therapy led to some improvements in quality of life scores, as well as more frequent use of inhaled corticosteroids and long-acting β-agonists, and less frequent use of short-acting β-agonists (one trial, 220 women). The FENO-based algorithm was associated with fewer infants with recurrent episodes of bronchiolitis in their first year of life, and a trend towards fewer episodes of croup for infants. Pharmacist-led management improved asthma control scores at six months (one trial, 60 women); PMR improved lung function and quality of life measures (one trial, 64 women). No other differences between comparisons were observed.

Authors' conclusions

Based on eight included trials, of moderate quality overall, no firm conclusions about optimal interventions for managing asthma in pregnancy can be made. Five trials assessing pharmacological interventions did not provide clear evidence of benefits or harms to support or refute current practice. While inhaled magnesium sulphate for acute asthma was shown to reduce exacerbations, this was in one small trial of unclear quality, and thus this finding should be interpreted with caution. Three trials assessing non-pharmacological interventions provided some support for the use of such strategies, however were not powered to detect differences in important maternal and infant outcomes. While a FENO-based algorithm reduced exacerbations, the effects on perinatal outcomes were less certain, and thus widespread implementation is not yet appropriate. Similarly, though positive effects on asthma control were shown with PMR and pharmacist-led management, the evidence to date is insufficient to draw definitive conclusions.

In view of the limited evidence base, further randomised trials are required to determine the most effective and safe interventions for asthma in pregnancy. Future trials must be sufficiently powered, and well-designed, to allow differences in important outcomes for mothers and babies to be detected. The impact on health services requires evaluation. Any further trials assessing pharmacological

interventions should assess novel agents or those used in current practice. Encouragingly, at least five trials have been identified as planned or underway.

PLAIN LANGUAGE SUMMARY

Interventions for managing asthma in pregnancy

Asthma is the most common disorder of the respiratory system (the organs that help you breathe) in pregnancy, affecting up to one in eight women. During pregnancy asthma can improve, worsen or remain unchanged. Poorly controlled asthma may lead to complications for mothers including pre-eclampsia (high blood pressure and protein in the urine), gestational diabetes (high blood glucose) and caesarean birth; complications for babies may include death, preterm birth (before 37 weeks of pregnancy) and being born low birthweight. Maintaining adequate control of asthma during pregnancy, including effective management and prevention of exacerbations, is the goal of management. In pregnancy, women may be concerned about risks of taking medications, and their health professionals may be uncertain about best management strategies.

This review aimed to assess how effective and safe different interventions are for managing asthma during pregnancy. We were able to include eight randomised controlled trials involving 1181 women and their babies. The trials were of moderate quality overall. Five trials assessed medications. Inhaled magnesium sulphate helped to reduce further exacerbations for women with acute asthma, and helped to improve their lung function (one trial of unclear quality, 60 women). For ongoing therapy for pregnant women with stable asthma, the effect of inhaled corticosteroids on asthma exacerbations was not clear (two trials, 155 women; but data only analysed from one trial, 60 women); no difference was seen in the chance of exacerbations when inhaled corticosteroids were compared with oral theophylline, however more women receiving theophylline stopped treatment because of side effects (one trial, 385 women). Three trials assessed non-drug interventions. Adjusting women's asthma medications according to how much nitric oxide they exhaled (their fraction of exhaled nitric oxide (FENO)) was shown to reduce exacerbations and improve their quality of life (one trial, 220 women). Progressive muscle relaxation improved women's lung function and quality of life (one trial, 64 women), and asthma management led by a pharmacist helped to improve asthma control (one trial, 60 women).

Overall, we did not find enough evidence of benefits and harms from the randomised trials to be sure about the best way to manage asthma in pregnancy, although some interventions were promising. We need larger, high-quality trials, which should report on important health outcomes for mothers and babies, including longer-term outcomes for babies into childhood and adulthood. Five trials are currently being planned or are underway assessing interventions for asthma in pregnancy.

BACKGROUND

Description of the condition

Introduction and definition

Asthma is the most common respiratory disorder complicating pregnancy. Although a reversible disease, asthma is potentially life threatening for a mother and her infant (Katz 2008). The prevalence of asthma in pregnant women appears to have increased over recent decades (Katz 2008); estimates vary from approximately 3% to 12% (Kwon 2003; Kwon 2006; McCusker 2011). A review of studies related to asthma exacerbations during pregnancy suggested that exacerbations requiring medical intervention occur in approximately 20% of asthmatic women, and approximately 6% require hospital admission (Murphy 2006).

The effect of pregnancy on asthma

Available data describe a variable course of asthma in pregnancy, influenced by both the severity of the pre-existing condition, and physiologic changes during pregnancy (Gluck 2004; Katz 2008). Asthma may improve, worsen or remain unchanged during pregnancy. A meta-analytic review of 14 studies assessing changes in the course of asthma throughout pregnancy suggested that approximately one-third of pregnant asthmatic women experience a symptomatic improvement, one-third experience a worsening,

and one-third remain the same (Juniper 1993). Later studies have suggested however, that this concept may underestimate the real risk of exacerbations during pregnancy (Katz 2008).

While a number of factors that may improve or worsen asthma have been noted, the mechanisms involved are largely undefined, and thus a woman's asthma course during pregnancy is often unpredictable (Schatz 1999). Consequently, it is essential that a pregnant woman with asthma be followed carefully, and managed appropriately.

The effects of asthma on pregnancy

Studies investigating the association between maternal asthma or exacerbations of asthma and adverse maternal and perinatal outcomes have revealed inconsistent findings (Katz 2008). Early retrospective data suggested asthma in pregnancy was associated particularly with an increased risk of neonatal death, low birthweight, preterm birth and pre-eclampsia (Bahna 1972). Subsequent retrospective and prospective studies have shown asthma in pregnancy to be associated with a range of complications - maternal adverse outcomes including pregnancy-induced hypertension (Enriquez 2007), pre-eclampsia (Demissie 1998; Enriquez 2007), gestational diabetes (Hodyl 2014), premature rupture of membranes (Hodyl 2014), caesarean birth (Demissie 1998; Dombrowski 2004a; Enriquez 2007) (including emergency caesarean birth) (Hodyl 2014), chorioamnionitis (Liu 2001), hyperemesis (Bahna 1972), and antepartum and postpartum haemorrhage (Enriquez 2007; Hodyl 2014). Adverse perinatal outcomes that have been linked with maternal asthma include perinatal mortality (Källén 2000), preterm birth (Breton 2009; Demissie 1998; Dombrowski 2004a; Källén 2000), low birthweight (Breton 2009; Demissie 1998; Enriquez 2007; Källén 2000; Murphy 2006), small-for-gestational age (Clifton 2009; Hodyl 2014), intrauterine growth restriction (Bahna 1972; Demissie 1998; Enriquez 2007; Källén 2000), and congenital malformations (Demissie 1998; Hodyl 2014). Recently, in a retrospective cohort study of over 220,000 singleton births, designed to assess the effects of maternal asthma on neonatal morbidity, asthma was shown to be associated with preterm birth (for each week after 33 completed weeks of gestation), small-for-gestational age, neonatal intensive care unit admission, hyperbilirubinaemia, respiratory distress syndrome, transient tachypnoea of the newborn and asphyxia; term infants were also shown to have an increased risk of intracerebral haemorrhage and anaemia (Mendola 2014).

A number of studies have failed, however, to demonstrate an association between asthma in pregnancy and adverse outcomes including low birthweight (Schatz 1995), perinatal mortality (Clifton 2009; Schatz 1995), preterm birth (Clifton 2009; Dombrowski 2004a; Enriquez 2007; Murphy 2006; Schatz 1995), pre-eclampsia (Dombrowski 2004a; Murphy 2006; Schatz 1995) and congenital malformations (Enriquez 2007; Källén 2000; Schatz 1995). Such discrepant data may be explained in part by the variation between studies in population characteristics such as asthma severity and treatment(s) women received, often making comparisons between studies difficult (Katz 2008). Variation in the proportions of male and female participants between studies (and failure to analyse by infant sex) may further explain inconsistencies in findings observed; a number of studies have suggested sex differences in adverse perinatal outcomes in women with asthma (Clifton 2009; Murphy 2005b).

Associated with the increased risk of being born preterm, children born to mothers with asthma during pregnancy may also be at an increased risk of long-term health complications associated with prematurity, including neurodevelopmental sequale (such as cerebral palsy or other motor impairments, sensory impairments such as visual and auditory deficits, intellectual/mental impairments; or other developmental 'lags' not classified as impairments) and behavioural sequale (such as dysfunction in other cognitive areas including attention, visual processing, academic progress, and executive function) (Saigal 2008). Short-term risks for babies born preterm include severe infections (neonatal sepsis), respiratory distress syndrome, jaundice, brain injury (most commonly intraventricular haemorrhage), necrotising enterocolitis, retinopathy of prematurity, and anaemia of prematurity (Lawn 2013).

A recent meta-analysis including 40 studies and involving over 1,600,000 women assessed the risk of adverse perinatal outcomes associated with maternal asthma and the size of these effects (Murphy 2011). This meta-analysis showed maternal asthma to be associated with an approximate 40% increased risk of both low birthweight and preterm birth, an approximate 50% increased risk of pre-eclampsia, and an approximate 20% increased risk of small-for-gestational age (Murphy 2011). An earlier meta-analysis showed asthma exacerbations during pregnancy to be associated with a more than doubled risk of low birthweight (Murphy 2006), however no increased risk of preterm birth nor pre-eclampsia was shown.

Investigations

Asthma diagnosis may be made by a history of asthma symptoms such as breathlessness, chest tightness, cough and sputum production, and the use of spirometry (Dombrowski 2006). In the initial assessment of a pregnant woman with asthma, and at regular visits, spirometry has been recommended (NAEPP 2005). Due to the potential for asthma severity to change throughout pregnancy, women with persistent asthma have been recommended to be evaluated monthly, including history, lung auscultation and assessment of pulmonary function (NAEPP 2005). For women with very poor asthma control, more frequent review has been recommended until control is achieved (NAEPP 2005).

Ultrasound is widely regarded as a useful tool for fetal surveillance in pregnancy. For women with sub-optimal asthma control, or moderate to severe asthma, more regular fetal ultrasound examinations from 32 weeks' gestation to monitor fetal growth, which may

be affected by uncontrolled asthma in pregnancy, has been suggested (NAEPP 2005). During and/or following a severe asthma exacerbation in pregnancy, fetal monitoring using ultrasound or cardiotocography has also been recommended (NAEPP 2005).

Description of the intervention

Interventions for managing asthma in pregnancy

Maintaining adequate control of asthma during pregnancy, including the effective management and prevention of exacerbations, is the goal of asthma management, shown to be associated with benefits for the mother and her infant (Bracken 2003; Murphy 2006; Schatz 1995). Asthma control during pregnancy has been defined, by the United States National Heart, Lung, and Blood Institute in their expert panel report as: minimal or no chronic symptoms day or night; minimal or no exacerbations; no limitations of activities; maintenance of (near) normal pulmonary function; minimal use of short-acting inhaled β2-agonists; minimal or no adverse effects from medications (NAEPP 2005).

A critical issue in considering the management of asthma in pregnancy, is whether the potential benefit for improving a mother's asthma control outweighs potential adverse effects of asthma interventions on her unborn infant. It must also be considered whether pregnancy itself alters the effects of asthma interventions, and thus whether, and how, the management of pregnant women with asthma should differ from asthma management in those who are not pregnant.

Interventions for managing asthma during pregnancy have the potential to not only improve maternal and perinatal health, but also to reduce associated healthcare costs, for example, through reducing asthma-related unplanned medical and emergency department visits for pregnant women, and reducing costs associated with the adverse maternal and neonatal outcomes linked to poorly controlled asthma (i.e. preterm birth and neonatal intensive care unit admissions).

The management of asthma in pregnant and non-pregnant individuals may involve both non-pharmacological and pharmacological interventions; often multiple inter-related strategies are employed to maintain optimal control. A recent Cochrane review *'Culture-specific programs for children and adults from minority groups who have asthma'* suggested some enhanced effectiveness of culture-specific programs for management for minority groups, as compared with generic programs, when considering most asthma outcomes in non-pregnant populations (Bailey 2009).

Pharmacological agents

Pharmacological therapy for asthma aims to control symptoms and achieve optimal lung function at the lowest effective doses of medication (NACA 2006).

Pharmacological medications for asthma can be broadly categorised as rescue agents and maintenance agents, or may alternatively be grouped according to their mechanism of action (anti-inflammatory agents and bronchodilators). Rescue agents are used on an 'as-needed basis' to treat acute symptoms; the most commonly used are short-acting β-agonists. Inhaled anticholinergics, such as ipratropium, can also be used for severe acute asthma (NACA 2006). Maintenance agents aim to prevent asthma symptoms and exacerbations, and include anti-inflammatory agents such as inhaled corticosteroids, along with long-acting bronchodilators (β-agonists). Less commonly used maintenance agents include mast cell stabilisers, leukotriene-receptor antagonists and theophylline (a sustained release methylxanthine).

The treatment of asthma during pregnancy with pharmacological medications has widely been considered 'safer' for a pregnant woman and her fetus than uncontrolled asthma and the associated symptoms and exacerbations (NAEPP 2005). While for many asthma medications there appear to be no, or minimal associated adverse effects during pregnancy (Bracken 2003; Dombrowski 2006; Liccardi 2003; NAEPP 2005), no Cochrane review has assessed the effects of pharmacological agents on maternal and fetal/infant morbidity, and the optimal pharmacological treatment strategies for pregnant women are unclear.

For example, while safety data on the use of inhaled short-acting β-agonists in pregnancy have been regarded as reassuring (NAEPP 2005), a number of epidemiological studies have suggested an increase in the risk of congenital abnormalities with the use of maternal bronchodilators, including short-acting β-agonists, anticholinergic agents and theophylline (Källén 2007; Lin 2008). The use of anti-inflammatory agents (including oral corticosteroids) to prevent acute exacerbations in pregnancy, has additionally been associated with an increased risk of cleft lip, cleft palate or both (Carmichael 2007; Park-Wyllie 2000; Rodríguez-Pinilla 1998). High doses of inhaled corticosteroids during the first trimester of pregnancy, as opposed to low to moderate doses, have also been associated with an increased risk of congenital malformations (Blais 2009). Other concerns surrounding the use of corticosteroids in pregnancy persist, with animal studies and observational data suggesting possible adverse effects on growth, risk of neonatal infection, fetal hypothalamo-pituitary-adrenal (HPA) function and neonatal blood pressure (Mildenhall 2006).There is a recognised potential that exposure to corticosteroids could program cardiovascular settings in the fetus, leading for example, to adult hypertension, dyslipidaemia, and insulin resistance or diabetes mellitus (Dalziel 2005). A recent study has however demonstrated that the use of inhaled corticosteroids by pregnant asthmatic women, does not affect fetal glucocorticoid regulated pathways; and thus the authors considered that it is unlikely that inhaled corticosteroids contribute to adverse effects on fetal growth and development (Hodyl 2011).

Women's concerns regarding the safety of pharmacological agents, and health professionals' lack of certainty (with inconsistent rec-

ommendations), have been shown to lead to 'under-dosing,' limited adherence to pharmacological treatments by pregnant women (Lim 2012a; Sawicki 2012), and potentially avoidable morbidity (Murphy 2006). It has been estimated that over one-third of women may discontinue their asthma medications during pregnancy, many without consulting their doctors; and up to one quarter of health professionals may instruct pregnant women to decrease or discontinue asthma medication during pregnancy due to lack of confidence and/or knowledge, despite asthma being well controlled by current therapy (Lim 2011a). In order to guide the optimal care of pregnant women, it is therefore essential that the effects of pharmacological agents used to manage asthma in pregnancy be formally evaluated.

Non-pharmacological interventions for asthma management in pregnancy

A multitude of non-pharmacological measures are often used in conjunction with pharmacological agents for the management of asthma. These include: the monitoring of lung function to guide treatment (e.g. the use of spirometry or serial peak-flow measurements); monitoring of airway inflammation to guide treatment (e.g. inflammometry - the use of sputum eosinophil counts and exhaled nitric oxide); lifestyle modification including the avoidance of triggers (such as smoking cessation); dietary interventions; physical interventions (e.g. breathing exercises; inspiratory muscle training); psychological interventions; educational programs; written asthma action plans; and combinations of strategies.

While a number of such interventions have been assessed for the management of asthma in the general population, little is known regarding their importance for the management of asthma in pregnancy, and how their effects differ for pregnant women.

Monitoring of lung function and airway inflammation

Monitoring of lung function in pregnancy has been considered a valuable component of asthma management, used to guide further treatment and intervention. Impaired pulmonary function during pregnancy has been associated with adverse perinatal outcomes, including gestational hypertension and prematurity (Schatz 2006). After initial assessment, follow-up measures of pulmonary function are preferably done by the use of spirometry; however peak-flow measurements have been considered adequate and allow the patient to monitor serial measurements of lung function at home (NAEPP 2005). It has been recommended that patients with moderate to severe asthma assess their lung function daily by peak-flow measurements (NAEPP 2005).

An alternative to the monitoring of lung function to guide asthma management in pregnancy is the monitoring of airway inflammation - such as measuring sputum eosinophil counts and the fraction of exhaled nitric oxide (FENO) (Petsky 2007; Petsky 2009). These interventions measure underlying airway inflammation, which is the target of inhaled corticosteroid therapy. A Cochrane review *'Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults'* assessing the use of FENO compared with clinical symptoms to tailor the dose of inhaled corticosteroids in the non-pregnant population, found no clear benefits to recommend the use of FENO-based management (Petsky 2009). The equivalent review *'Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults'* assessing tailored interventions based on sputum eosinophils did however, support benefits with the use of this technique for adults with frequent exacerbations and severe asthma (Petsky 2007).

It is currently unknown whether similar effects are seen for pregnant women with the use of such techniques; no Cochrane review has assessed methods for monitoring lung function or airway inflammation for improving asthma management in pregnant women.

Diet, exercise and lifestyle modifications

Avoiding exposure to environmental triggers has been widely considered an important component in the management of asthma (Dombrowski 2006). Triggers may include animals, dust mites, pollens, molds, air pollutants, food additives (e.g. sulphites), certain drugs and tobacco smoke (Dombrowski 2006). A number of Cochrane reviews have assessed control measures for asthma management in the general population (Campbell 2000; Gøtzsche 2008; Kilburn 2001; Singh 2002), however, the importance of such measures for pregnant women is unclear. Smoking cessation in particular has been considered important for both asthmatic and non-asthmatic pregnant women. During pregnancy, asthma exacerbations have been shown to be more common and more severe in smokers than in non-smokers; such exacerbations may in turn be associated with maternal and perinatal complications, and thus the risk of maternal asthma may be greater for smokers (Murphy 2010). A recent retrospective analysis has shown that while maternal asthma and cigarette smoking during pregnancy are both independently associated with adverse perinatal outcomes, combined, they compound the risk particularly of preterm birth and urinary tract infection (Hodyl 2014). The cessation of smoking in pregnant asthmatic women for improving pregnancy outcomes has, however, not been formally assessed.

In addition to environmental triggers, it is believed that food additives (such as sulphites) may trigger asthma symptoms (Liccardi 2003), and thus their avoidance may improve management. Other dietary modifications that have been assessed for asthma management in the general population include dietary supplements (Allam 2004; Kaur 2009; Thien 2002), sodium (Pogson 2011) and marine fatty acid manipulation (Thien 2002). A calorie controlled diet for asthma management has also been assessed in the general population (Cheng 2003).

A number of physical interventions have been evaluated for

asthma management in the non-pregnant population, including breathing exercises (Holloway 2004), inspiratory muscle training (Ram 2003), manual therapies (Hondras 2005), physical training (Chandratilleke 2012), and yoga (Posadzki 2011). While the benefits of exercise during pregnancy are now recognised, and women are thus encouraged to engage in 'light-to-moderate' exercise in the absence of any known pregnancy or medical complications (ACOG 2002), the benefits and risks for asthmatic pregnant women are unclear.

Complementary and alternative medicines

Homoeopathy is a commonly used complementary treatment for asthma. It is a complementary healing system, based on 'curing like with like;' a substance which gives rise to specific symptoms, when given in pharmacological doses to healthy individuals, can be used to treat patients presenting with the same symptoms (McCarney 2004). Other common complementary and alternative medicinal therapies used in the management of asthma include herbal remedies (e.g. plants and plant extracts) (Arnold 2008).
Studies have suggested that common reasons pregnant women may choose to take or turn to herbal remedies and other complementary and alternative therapies, include their perceived safety and effectiveness, personal control, accessibility, and the holistic nature of the treatment (Holst 2009; Westfall 2003). While homoeopathy (McCarney 2004), and other complementary and alternative therapies, including acupuncture (McCarney 2009), chiropractic techniques and osteopathy (Hondras 2005), have been assessed in the general population for the treatment of chronic asthma, their place in the management of asthma in pregnancy is unclear.

Psychological interventions

The effectiveness of psychological therapies for the management of asthma in the general population is currently uncertain (Yorke 2006). During pregnancy, it has been suggested that women with asthma should have access to regular contact with their healthcare provider, for the provision of adequate psychological support, for reassurance and for the reduction of emotional stress (Liccardi 2003). The effects of specific psychological interventions (such as cognitive therapy, behavioural therapy, relaxation therapy, biofeedback therapy and 'supportive' counselling) for asthma management in pregnancy have however, not been formally reviewed.

Self-management of asthma including asthma action plans

Self-management of asthma may incorporate a range of strategies - including education, self-monitoring, regular review by a health professional and the use of written asthma action plans (Gibson 2004), aimed at improving adherence to medication regimens and encouraging patients to seek prompt attention for exacerbations. Patient education or educational programs as a component of self-management plans, have been recognised as an important aspect in the control of asthma, and may include information regarding the recognition of symptoms, the avoidance of triggers, self-monitoring and correct peak expiratory flow rate (PEFR) measurement, the appropriate use of medication, and advice regarding when to seek medical attention (Dombrowski 2006; Gibson 2002; Liccardi 2003; Tapp 2007). Written asthma action plans are individualised plans produced for the purpose of patient self-management of asthma and its exacerbations. The plans are tailored to assist individuals in managing their asthma based on symptoms and/or peak flow measurements, and may include information on how to recognise worsening asthma, how to act promptly to prevent asthma worsening (including how to modify medications), and what to do in an emergency (including seeking access to medical care) (Gibson 2004; GINA 2001). While the use of limited asthma education (information only) was shown in a Cochrane review to not improve health outcomes in the general population (Gibson 2002), in the Cochrane review '*Self-management education and regular practitioner review for adults with asthma*', self-management plans that enabled individuals to adjust their medication using a written action plan were shown to be more effective than other forms of self-management in the general population (Gibson 2002). While asthma action plans have been recognised as a critical component for the management of asthma in many nations, and comprise part of the recommendations for optimum care as devised by the Global Initiative in Asthma (GINA) (GINA 2001), studies from Australia and the United Kingdom have suggested declining use despite evidence of clinical benefit (Jones 2000), and unpopularity with both patients and clinicians has been noted (Ruffin 2001).
Findings from observational studies have provided support for the need for self-management skills and the effectiveness of asthma education for women during pregnancy (Murphy 2005a). A prospective cohort study in Australia assessed asthma self-management skills and knowledge among a group of 211 pregnant women. Women received education about asthma control and management skills, including trigger avoidance and smoking cessation where appropriate. Prior to education, approximately 40% of women reported non-adherence to inhaled corticosteroids, and inhaler technique was assessed as inadequate for 16%; only 15% had a written action plan, and 3% performed peak flow monitoring. Following asthma education, significant improvements were shown in all aspects of asthma self-management; severe asthma, night symptoms, and reliever medication use were also shown to be significantly reduced (Murphy 2005a).
While asthma education and management programs have traditionally been delivered in hospital settings such as antenatal clinics, and by physicians and general practitioners, the role for other health professionals including community-based pharmacists in assisting asthma management, is increasingly being assessed. A number of recent studies have supported the utility of community pharmacy-based programs that provide education surrounding inhalation technique and medication adherence, in improving

asthma control and therapeutic outcomes in adult asthmatic patients (Basheti 2007; Mehuys 2008). The value of such community-based self-management programs, and the delivery of education by health professionals not traditionally involved in asthma management for pregnant women, is currently unclear.

While self-management plans including the use of written asthma action plans, have been associated with improved asthma outcomes in adults (Abramson 2001; Gibson 2002), their effects are likely highly dependent upon the population. Studies have suggested that pregnant women may benefit from self-management education as part of their obstetric care (Murphy 2005a) however, no systematic review has formally assessed the effectiveness of such education, nor the use of written asthma action plans.

Why it is important to do this review

Asthma is the most common respiratory disorder complicating pregnancy, and has been associated with a range of adverse maternal and perinatal outcomes. There is strong evidence however, that the adequate control of asthma in pregnancy is associated with improved health outcomes for both the mother and her infant; accordingly effective management interventions have the potential to reduce healthcare costs otherwise associated with poorly controlled asthma. Despite the known risks of poorly controlled asthma during pregnancy, it has been shown that a large proportion of pregnant women have sub-optimal asthma control, due to concerns particularly surrounding the risks of pharmacological agents, and due to uncertainties regarding the effectiveness and safety of different management interventions or strategies.

To date, no Cochrane review has evaluated the effectiveness and safety of any of the known management interventions for asthma in pregnancy. This systematic review will therefore assess interventions (both pharmacological and non-pharmacological) used to manage asthma during pregnancy, to strengthen the link between the best current evidence and the optimal care of asthmatic pregnant women.

OBJECTIVES

The aim of this review is to systematically assess the effects of interventions (pharmacologic and non-pharmacologic, including self-management interventions) for managing women's asthma in pregnancy on maternal and fetal/infant outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished and ongoing randomised controlled trials with reported data. We planned to include quasi-randomised trials and cluster-randomised trials. We have included studies published as abstracts only. We included multi-armed trials along with two armed trials. Cross-over trials were not eligible for inclusion.

Types of participants

We included pregnant women with current asthma (with a health professional's diagnosis), regardless of gestational age, parity, plurality, and severity of asthma.

Types of interventions

We included any intervention used to manage asthma in pregnancy, compared with a placebo, with no intervention (i.e. standard care), or with an alternative intervention for managing asthma. We also included any intervention used to manage asthma in a population of reproductive age which included a subset of pregnant women (where data have been reported separately for the subset of pregnant women).

We included both pharmacological interventions and non-pharmacological interventions (along with combined interventions).

Pharmacological interventions, may have included, for example, the use of rescue agents (e.g. short-acting β-agonists, and inhaled anticholinergics) and maintenance agents (e.g. inhaled corticosteroids, long-acting β-agonists, leukotriene-receptor antagonists, mast cell stabilisers, sustained release methylxanthines and systemic steroids).

Non-pharmacological interventions may have included any strategy (as described in the Background, such as monitoring of lung function and airway inflammation; diet, exercise and lifestyle modifications; complementary and alternative medicines; psychological interventions; self-management plans) aimed at improving the management of asthma during pregnancy, and any combination of strategies.

Types of outcome measures

We considered maternal and fetal/neonatal/infant outcomes relating to effectiveness and safety of the interventions.

Primary outcomes

For the mother

- Asthma exacerbations (as defined by trialists, e.g. events for which the woman sought medical attention - an unscheduled visit to a doctor, presentation to the emergency room, admission to hospital or where oral corticosteroids were used for treatment)

For the neonate/infant

- Admission to neonatal intensive care unit or special care nursery

Secondary outcomes

For the mother

- Asthmatic symptoms (e.g. including episodes of wheeze, shortness of breath, symptoms scores, i.e. measures of dyspnoea or breathlessness with Borg score, Visual Analogue Scale, the Asthma Control Questionnaire score (ACQ), symptom-free days)
- Asthma medication requirements (e.g. use of rescue medication, use of preventer medication)
- Lung function (e.g. peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV1), forced vital capacity (FVC))
- Inflammatory markers (e.g. serum and sputum eosinophils, serum eosinophilic cationic protein (ECP), exhaled nitric oxide)
- Asthma self-management skills (e.g. inhaler technique, correct knowledge of medication requirements)
- Quality of life (e.g. measured using a validated health-related generic and/or disease specific quality of life questionnaire)
- Days/time lost from work or school
- Pregnancy-induced hypertension
- Pre-eclampsia/eclampsia
- Gestational diabetes
- Caesarean birth
- Antepartum haemorrhage
- Postpartum haemorrhage
- Preterm prelabour ruptured membranes
- Preterm labour
- Chorioamnionitis
- Hyperemesis
- Adverse effects (clinical or biochemical) attributed to intervention and discontinuation of the intervention due to adverse effect(s)
- Adherence with intervention

Whenever possible, we planned to include change from baseline data for relevant secondary maternal outcomes (i.e. for asthmatic symptoms; asthma medical requirements; measures of lung function; inflammatory markers; and quality of life).

For the fetus/neonate

- Termination of pregnancy
- Stillbirth
- Neonatal death
- Gestational age at birth
- Preterm birth (less than 32 weeks; less than 37 weeks)
- Birthweight
- Low birthweight (less than 2500 g)
- Small-for-gestational age (less than the 10th centile for gestational age)
- Apgar score of less than seven at five minutes
- Need for active resuscitation (assisted ventilation via an endotracheal tube) at birth
- Respiratory distress syndrome*
- Intraventricular haemorrhage*
- Periventricular leukomalacia*
- Chronic lung disease*
- Necrotising enterocolitis*
- Retinopathy of prematurity*
- Patent ductus arteriosus*
- Hypothalamo-pituitary-adrenal (HPA) axis function (however defined by authors)*
- Hyperbilirubinemia*
- Jaundice
- Neonatal sepsis
- Congenital malformation

For the infant, child, and for the child as an adult

- Death*
- Any neurodevelopmental disability (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or development delay/intellectual impairment (defined as developmental quotient or intelligence quotient more than 2 standard deviations below population mean))*
- Growth assessments (weight, head circumference, length, skin fold thickness, body mass index)*
- Lung function*
- Respiratory morbidity (including bronchiolitis, croup, asthma) (however defined by authors)*
- Blood pressure*
- Glucose intolerance/insulin sensitivity (however defined by authors)*
- Dyslipidaemia (however defined by authors)*
- HPA axis function (however defined by authors)*
- Age at puberty*
- Bone density*
- Visual impairment (however defined by authors)*
- Hearing impairment (however defined by authors)*
- Developmental delay (defined as developmental quotient more than 2 standard deviations below population mean)*
- Intellectual impairment (defined as intelligence quotient more than 2 standard deviations below population mean)*
- Cerebral palsy (however defined by authors)*
- Motor delay or impairment (however defined by authors)*
- Educational achievement (completion of high school, or however defined by authors)*
- Behavioural/learning difficulties (however defined by authors)*

Use of health services

- Antenatal admissions to hospital for the mother and length of stay
- Emergency department visits for the mother
- Admission to intensive care unit for the mother
- Length of postnatal hospitalisation for the mother
- Length of neonatal hospitalisation for the infant
- Costs of care for the mother or baby or both

* Outcomes not pre-specified at the protocol stage. We have also reported on composite outcomes not clearly defined in the included trials that may have included our pre-specified outcomes: *"obstetric complications"; "perinatal complications"*; *"healthy children delivered"*; *"other adverse outcomes."* We have clearly reported these as outcomes 'not pre-specified at protocol stage.'

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (2 June 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we contacted the Trials Search Co-ordinator of the Cochrane Airways Group to search their Trials Register (4 June 2014), see: Appendix 1.

We did not apply any language restrictions.

Data collection and analysis

The methods of data collection and analysis are adapted from the Cochrane Pregnancy and Childbirth Group's standard methods text.

Selection of studies

Two review authors (EB and KP) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author (PM).

We created a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors (EB and KP) independently extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author (PM). We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (EB and KP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor (PM).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should have produced comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed

whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to have affected results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we have presented results as summary risk ratio (calculated using the Mantel-Haenszel method) with 95% confidence intervals.

Continuous data

For continuous data, we have reported the mean difference (with 95% confidence intervals) where outcomes were measured in the same way between trials. If we had identified trials that measured the same outcome using different methods, we planned to use and report the standardised mean difference (with 95% confidence intervals).

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. In future updates of this review, if we include cluster-randomised trials, we plan to adjust their sample sizes if required using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we plan to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We plan to also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

We considered cross-over trials inappropriate for this research question, given that women's asthma courses during pregnancy are variable and often unpredictable (i.e. asthma in pregnancy is not a stable chronic condition), and also given the irreversible nature of many of the chosen review outcomes (for example, stillbirth/neonatal death and congenital malformations).

Multi-armed trials

We included a multi-armed trial (Wendel 1996). We have recorded and included all outcome data in the review as two-arm comparisons. We have included the data for the different arms in independent two-arm comparisons in separate meta-analyses.

Had we been unable to include the data in separate comparisons, we planned to combine them to create a single pair-wise comparison (Higgins 2011). If the control group was shared by two or more study arms, we planned to divide the control group between relevant subgroup categories to avoid double-counting the participants (for dichotomous data, we planned to divide the events and the total population, while for continuous data, we planned to assume the same mean and standard deviation (SD) but planned to divide the total population). We have described the details in the 'Characteristics of included studies' table.

Multiple pregnancies

As infants from multiple pregnancies are not independent, in future updates of this review, if trials involving multiple are included, we plan to use cluster-trial methods in the analyses, where the data allow, and where multiples make up a substantial proportion of the trial population, to account for non-independence of variables (Gates 2004).

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we have attempted to include all participants randomised to each group in the analyses, and all participants have been analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in a meta-analysis, we plan to investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where there

was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or where substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not have combined trials.

Where we have used random-effects analyses, the results have been presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

We performed separate comparisons for different types of interventions. We planned to consider separately, where possible:

- different classes of asthma medications (e.g. we planned to have separate comparisons for β-agonists (considering short-acting and long-acting separately); corticosteroids (considering inhaled and systemic (oral) steroids separately); leukotriene-receptor antagonists; anticholinergics; mast cell stabilisers, sustained release methylxanthines);
- dietary interventions;
- physical interventions;
- psychological interventions.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. Where we identified substantial heterogeneity we considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We planned to carry out the following subgroup analyses.

Maternal characteristics

- Severity of the woman's asthma (e.g. mild versus moderate; mild versus severe) (as defined by trialists).
- Smoking history (e.g. current or ex-smoker versus never smoked).

Characteristics of the intervention

For each pharmacological intervention (i.e. for each asthma medication class discussed above, and for complementary or alternative medicines where appropriate):

- specific agent (for example, when considering inhaled corticosteroids: beclomethasone versus budesonide versus fluticasone; or when considering short-acting β-agonists: salbutamol versus terbutaline);
- dose (i.e. low versus high; for example, when considering dosage of inhaled corticosteroids (HFA-beclomethasone equivalent): low daily dose ($\leq$ 400 mcg) versus medium daily dose (> 400 to 600 mcg) versus high daily dose (> 600 mcg).

For non-pharmacological interventions (e.g. dietary, physical, psychological interventions):

- intensity of the intervention (e.g. provision of information only versus educational sessions and regular review with a health professional).

For both:

- duration of the intervention (e.g. short versus long);
- timing of the intervention (e.g. commencement in the first trimester versus third trimester).

We planned to use only primary outcomes in subgroup analyses. We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We planned to report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Due to the large number of different comparisons, and paucity of data, however, we were unable to perform the pre-specified subgroup analyses.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effects of trial quality assessed by allocation concealment and random sequence generation, by omitting studies rated as inadequate ('high risk of bias') (including quasi-randomised trials) or 'unclear risk of bias' for these components. We planned to restrict this to the primary outcomes. However due to the large number of different comparisons, paucity of data, and unclear methodological quality of a number of the included trials, we were unable to perform sensitivity analyses.

In future updates of this review, we plan to investigate the impact of including studies with high levels of missing data, and the effects of any assumptions made such as the value of the ICC used for cluster-randomised trials, should they be included, using sensitivity analyses.

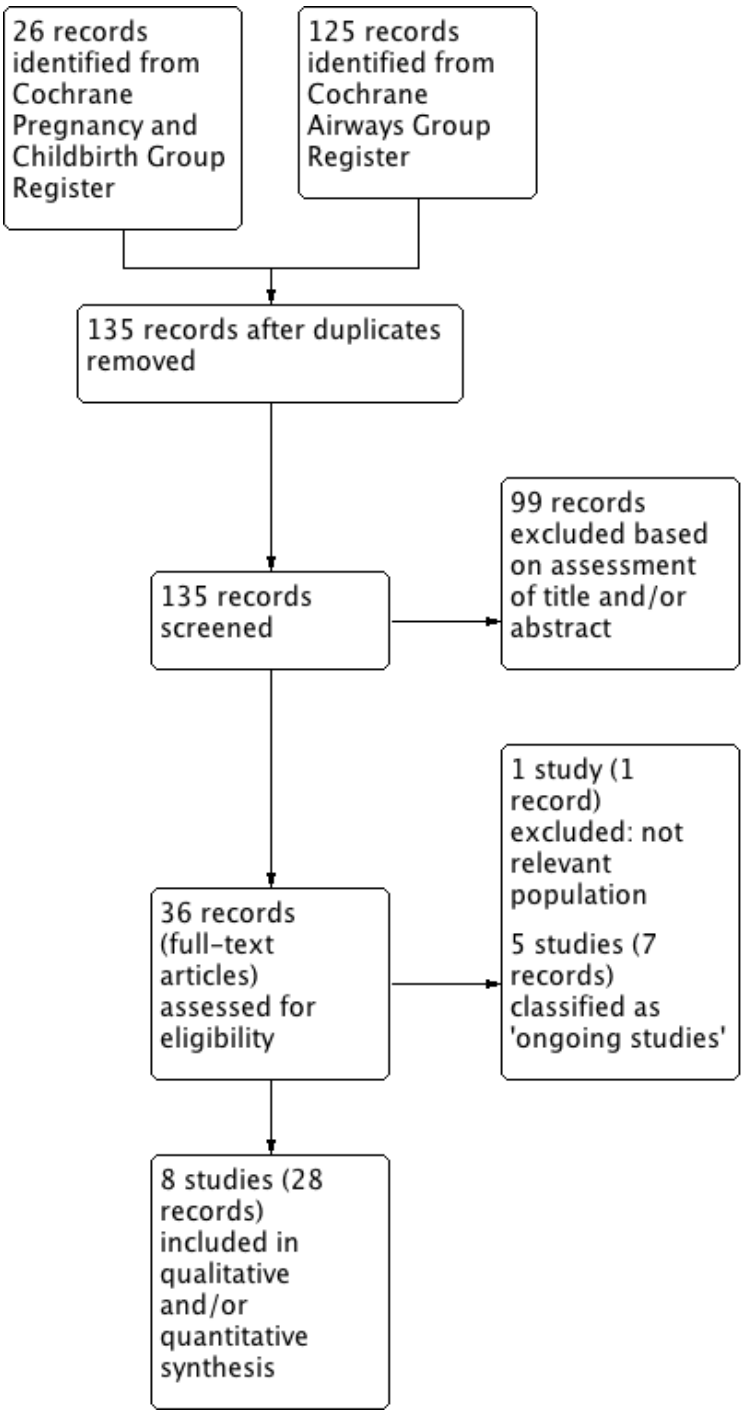
RESULTS

Description of studies

Results of the search

The Pregnancy and Childbirth Group's Register search retrieved 26 records and the Cochrane Airways Group's Trials Register search retrieved 125 records (see Figure 1). Following removal of duplicates, the titles and/or abstracts of 135 records were screened, and 99 records were excluded.

Figure 1. Study flow diagram.



We assessed 36 full-text records for eligibility, and included eight trials (Badawy 2012; Caramez 1998; Dombrowski 2004; Lim 2012; Nickel 2006; Powell 2011; Silverman 2005; Wendel 1996) (28 records), excluded one study (Schonberger 2004) and five studies (seven records) (ACTRN12613000244707; ACTRN12613000301763; ACTRN12613000800729; ACTRN12613000202763; NCT01345396) were classified as ongoing.

Information for the Caramez 1998 trial has to date been obtained from a published trial abstract only.

For further details, see Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Included studies

We have included eight trials, involving 1181 women and their babies in this review (Badawy 2012; Caramez 1998; Dombrowski 2004; Lim 2012; Nickel 2006; Powell 2011; Silverman 2005; Wendel 1996). The trials were conducted across a number of different countries, and settings, including in Brazil (Caramez 1998), the United States (Dombrowski 2004; Wendel 1996), Egypt (Badawy 2012), Germany (Nickel 2006) and Australia (Lim 2012; Powell 2011). One trial (Silverman 2005) recruited women from 32 different countries.

The eight trials assessed a variety of different interventions for the management of asthma during pregnancy, and women were randomised to a variety of pharmacologic interventions (Badawy 2012; Caramez 1998; Dombrowski 2004; Silverman 2005; Wendel 1996) and non-pharmacologic interventions (Lim 2012; Nickel 2006; Powell 2011).

Four trials assessed inhaled corticosteroids for asthma management in pregnancy (Caramez 1998; Dombrowski 2004; Silverman 2005; Wendel 1996); however they utilised different treatment regimens and had different comparisons.

In Caramez 1998, 95 pregnant asthmatic women were randomised to receive either *"1 mg/day of inhaled beclomethasone"* in addition to an inhaled bronchodilator and a tapered oral corticosteroid (prednisolone) during exacerbations (n = 49), or to the inhaled bronchodilator and tapered oral corticosteroid (prednisolone) alone (n = 46).

Wendel 1996 recruited 65 pregnancy women presenting with acute asthma exacerbations, and randomised them at two timepoints, thus assessing four different management strategies. Firstly, women requiring inpatient management with a FEV1 less than 70% after sequential bronchodilator therapy (isoetharine), were randomised to receive either intravenous aminophylline (5 mg/kg loading dose, then 0.5 mg/kg maintenance), intravenous corticosteroid (methylprednisolone 1 mg/kg every eight hours) (maximum single dose 80 mg) and an inhaled bronchodilator (albuterol) (n = 33), or to receive the intravenous corticosteroid (methylprednisolone) and an inhaled bronchodilator (albuterol) only (n = 32). At discharge, similar to in Caramez 1998, women were randomised to receive inhaled beclomethasone (metered dose, four puffs twice daily), an inhaled bronchodilator (albuterol metered dose inhaler) and an oral corticosteroid taper (methylprednisolone) (n = 34), or to receive the inhaled bronchodilator and an oral corticosteroid taper (methylprednisolone) alone (n = 31).

In Dombrowski 2004 inhaled beclomethasone was similarly assessed, however it was compared with oral theophylline for women with moderate asthma; 398 women were randomised to receive either inhaled beclomethasone (four puffs three times per day) in combination with a placebo pill (n = 194), or to theophylline pills (initial dose of 200 mg morning and evening; increased to 300 mg two times per day after three days) and a placebo inhaler (n = 191). All women were also supplied with an inhaled bronchodilator (albuterol) to be used on an 'as needed' basis.

In Silverman 2005, rather than beclomethasone, the inhaled corticosteroid budesonide was assessed. Once-daily inhaled budesonide (400 µg) in addition to usual treatment (n = 102) was compared with once-daily inhaled placebo (n = 117) for the management of mild-to-moderate asthma. The data included in this review from the Silverman 2005 trial, relate to the 219 pregnancies that were reported from 7241 participants included in the START trial (inhaled Steroid Treatment As Regular Therapy).

Inhaled magnesium sulphate was assessed in the Badawy 2012 trial of 60 women with acute asthma during pregnancy. Women were randomised to receive either routine treatment for acute asthma exacerbations (that included the inhaled bronchodilator, salbutamol) and inhaled magnesium sulphate (500 mg, 1 mL) (n = 30), or to routine treatment alone for acute asthma exacerbations (n = 30). In both groups, women received *"three sets of nebulization"*.

Corticosteroids were also utilised in Powell 2011, however in this trial, 220 pregnant asthmatic women were randomised to have their usual asthma therapy (inhaled corticosteroids (budesonide) and long-acting β-agonist therapy (salbutamol/formoterol)) adjusted according to an algorithm based on fractional exhaled nitric oxide measurements (FENO) (n = 111), or to an algorithm based on clinical practice guidelines (n = 109) during the second and third trimesters of pregnancy. In Powell 2011, the FENO-based algorithm used a sequential process: first, the FENO concentration was used to adjust the dose of inhaled corticosteroids; and second, the Asthma Control Questionnaire (ACQ) score was used to adjust the dose of long-acting β-agonist therapy (for further details of the intervention and control algorithms see Additional Table 1; Table 2; Table 3; Table 4).

In Lim 2012, similar to Powell 2011, pregnant women were randomised to different asthma management strategies. Sixty women were randomised to either a pharmacist-led 'Multi-disciplinary Approach to Management of Maternal Asthma (MAMMA) (n = 30), or to usual care (which did not include any additional monitoring or education sessions) (n = 30). Women in the intervention group experienced a collaborative approach to their asthma management (involving family, physicians and asthma educators), in which asthma education, monitoring, feedback and follow-up

were components of the monthly intervention. Women received pharmacist-led management reviews (which included administration of the ACQ, and questions about oral corticosteroid use, asthma related admissions, days off work and preventer/reliever use); if during review the ACQ scores increased by 0.5 or there had been a documented exacerbation, pharmacists and physicians collaborated on 'step-up' therapy. Women were also given a hand-held device (and instructions) to use for home monitoring of lung function.

Finally, in the Nickel 2006 trial, progressive muscle relaxation (PMR) for the management of asthma was assessed in 64 pregnant women with bronchial asthma. Women were randomised to receive PMR sessions (30-minute group sessions, three times per week for eight weeks) (n = 32) or to receive sham training sessions (also 30-minute sessions, three times per week) (n = 32). In the PMR sessions, women were instructed to deliberately apply tension to certain muscle groups then release the tension and focus on how the muscles relaxed during the process; women also received precise instructions for daily practice at home (15 minutes, two times a day using a shortened form of the procedure).

Excluded studies

We excluded one trial from this review (Schonberger 2004), as the unit of randomisation was 'the family' and this trial included both pregnant and non-pregnant women; data for pregnant women alone could not be extracted.

Risk of bias in included studies

Summaries for the risk of bias of the included studies are given in Figure 2 and Figure 3. Overall we judged two trials to be at a low risk of bias, two trials to be at an unclear risk of bias, and the other four trials to be at a moderate risk of bias.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

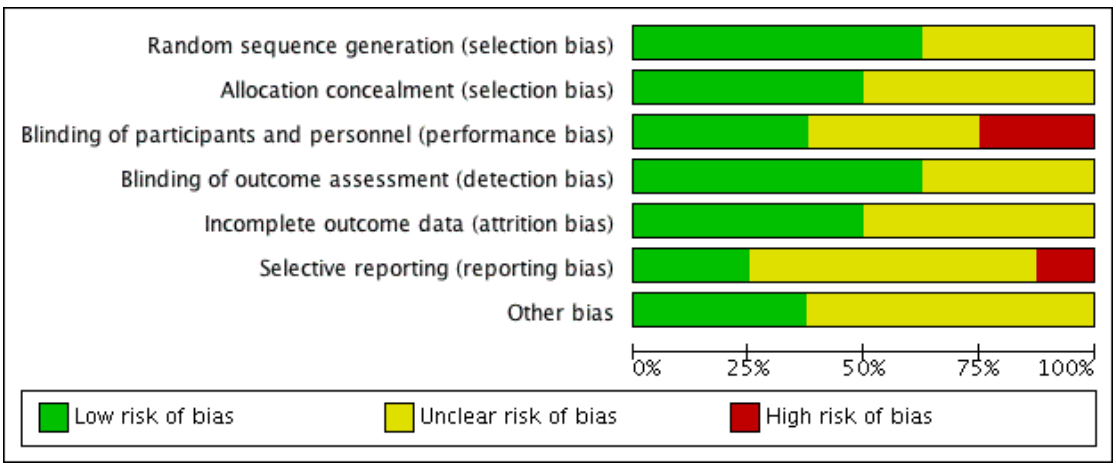
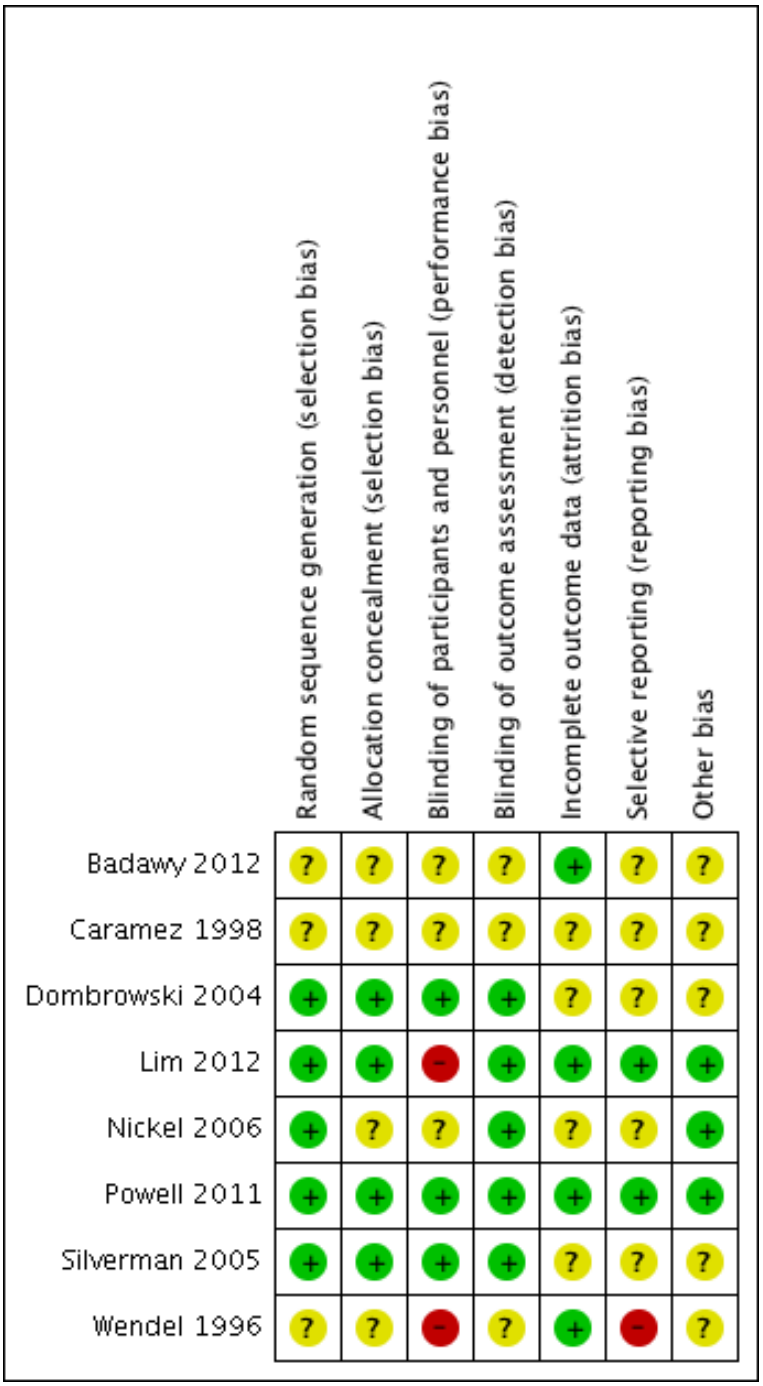


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Five of the included trials were judged to have used adequate methods to generate their random sequence (Dombrowski 2004; Lim 2012; Nickel 2006; Powell 2011; Silverman 2005). In Dombrowski 2004, the sequence was generated by the co-ordinating centre using the simple urn model; while in Lim 2012, Nickel 2006, Powell 2011 and Silverman 2005, random number sequences were computer-generated. In the remaining three trials (Badawy 2012; Caramez 1998; Wendel 1996), the methods used to generate the random sequence were not described, and thus the risk of selection bias was judged as unclear.

In four of the trials, methods to conceal allocation were judged to be adequate (Dombrowski 2004; Lim 2012; Powell 2011; Silverman 2005). Dombrowski 2004 used sequentially numbered medication kits; Lim 2012 used sequentially numbered, sealed, opaque envelopes; in Powell 2011, an algorithm keeper, not directly involved in assessment or care of women, concealed the treatment algorithm group from women and study personnel; and Silverman 2005 used central randomisation (at the sponsor's site by a person not involved in the analysis of data). In the other four trials (Badawy 2012; Caramez 1998; Nickel 2006; Wendel 1996), the methods to conceal allocation were not described in sufficient detail, and thus the risk of selection bias was judged as unclear.

Blinding

In three trials the risk of performance and detection bias were both judged to be low (Dombrowski 2004; Powell 2011; Silverman 2005). In Dombrowski 2004 and Silverman 2005, a placebo was used to blind women, study personnel and outcome assessors (Dombrowski 2004: women received inhaled beclomethasone and placebo pills or inhaled placebo and theophylline pills; Silverman 2005: women received inhaled budesonide or inhaled placebo). In Dombrowski 2004, while serum theophylline concentrations were obtained for treatment regulation, samples were taken from women in both groups. These samples were assessed by the Biostatistics Co-ordinating Centre who provided study investigators with instructions to increase or decrease the dose of theophylline pills; to maintain blinding, they also 'adjusted' the dose of placebo pills. In Powell 2011, women and study personnel were blinded, with the research assistant who collected data at monthly appointments sending data to an 'algorithm keeper', who applied the relevant algorithm and sent treatment recommendations to the research assistant; outcome assessors were also blind to group allocation.

Two trials were judged to be at a high risk of performance bias; the use of a placebo was not detailed in Wendel 1996, and it was not possible due to the nature of the intervention, to blind women/study personnel in Lim 2012. The remaining three trials were judged to be at an unclear risk of performance bias (Badawy 2012; Caramez 1998; Nickel 2006). In Badawy 2012 and Caramez 1998, insufficient information was available to determine risk of bias, and in Nickel 2006, while sham training was used, it was unclear as to whether this would have been successful in blinding women (with instructions in sham sessions and PMR session differing), and study personnel administering the training could not be blinded. While the risk of performance bias was judged as high and unclear in Lim 2012 and Nickel 2006 respectively, both trials were judged to be at a low risk of detection bias with outcome assessors reported to be blind to group allocation. In Badawy 2012, Caramez 1998 and Wendel 1996 there was insufficient information to confidently determine risk of detection bias.

Incomplete outcome data

Four trials (Badawy 2012; Lim 2012; Powell 2011; Wendel 1996) were judged to have a low risk of attrition bias. In Powell 2011, while 11/111 women withdrew from the FENO group after randomisation and 6/109 withdrew from the control group, withdrawals were for similar reasons, and all women were included in the final analyses (with the final visit before withdrawing counted as the 'end of study' visit); in Wendel 1996, no women were lost to follow-up or excluded during the inpatient phase of the trial, and in the outpatient phase, one woman out of 34 women in the intervention group was lost to follow-up and 4/31 women from the control group were lost to follow-up; no other exclusions were detailed. In Lim 2012, one woman in each group (2/60) was lost to follow-up.

For the other four trials, the risk of attrition bias was judged to be unclear (Caramez 1998; Dombrowski 2004; Nickel 2006; Silverman 2005).

Selective reporting

Two trials, Lim 2012 and Powell 2011, were judged to be at a low risk of reporting bias, with data reported for all expected outcomes (as per the trial protocol and registration respectively). For one trial (Wendel 1996), the risk of reporting bias was judged to be high, with perinatal and obstetric outcome data reported overall only (including some women who were not randomised and were managed as outpatients).

For the remaining five trials (Badawy 2012; Caramez 1998; Dombrowski 2004; Nickel 2006; Silverman 2005), there was insufficient information available to confidently assess selective reporting and thus the risk of reporting bias was judged to be unclear.

Other potential sources of bias

In Nickel 2006, Lim 2012 and Powell 2011, groups were well balanced at baseline, and no other obvious sources of bias were identified. The other five trials (Badawy 2012; Caramez 1998; Dombrowski 2004; Silverman 2005; Wendel 1996) were judged to be at an unclear risk of other potential sources of bias. In Badawy 2012 and Caramez 1998, there was insufficient information available to determine risk of other bias; the Caramez 1998 trial has been published in abstract form only; and while in the Badawy 2012 trial it was reported that *"both groups were comparable"*, data were only reported on age, education, parity and duration of pregnancy, and no information was available for example, on baseline level of asthma control. In Silverman 2005 and Wendel 1996, baseline characteristics by group were not reported. In Dombrowski 2004, the frequency of self-reported smoking was significantly higher in the theophylline group. The authors of Dombrowski 2004 also reported that after an interim data review, it became apparent that the frequency of the primary outcome was below that projected; thus to increase the primary outcome, the eligibility requirements for the trial were changed after enrolment of 311 women to increase the frequency of the primary outcome (by only including women who required regular asthma treatment).

Effects of interventions

Eight trials, involving 1181 women and their babies were included. Due to the variety of different interventions assessed and comparison groups used in the included trials, the results are presented under seven different comparisons.

1. Inhaled magnesium sulphate versus control (for acute asthma)
2. Intravenous theophylline versus control (for acute asthma)
3. Inhaled corticosteroid versus control
4. Inhaled corticosteroid versus oral theophylline
5. FENO algorithm versus clinical guideline algorithm to adjust asthma therapy
6. Pharmacist-led multi-disciplinary approach to management of maternal asthma (MAMMA) versus standard care
7. Progressive muscle relaxation (PMR) versus sham training

1. Inhaled magnesium sulphate versus control (for acute asthma)

One trial involving 60 women was included in this comparison (Badawy 2012).

Primary outcomes

Maternal

In Badawy 2012, the addition of magnesium sulphate (500 mg (1 mL)) to routine treatment for acute asthma exacerbations (which included inhaled salbutamol (1 mL salbutamol solution dissolved in 8 mL normal saline)) (women in both groups received *"three sets of nebulization"*) was shown to significantly reduce the frequency of acute asthma exacerbations until birth (mean difference (MD) -2.80; 95% confidence interval (CI) -3.21 to -2.39; 60 women) (Analysis 1.1). The mean frequency of acute exacerbations was 0.4 (standard deviation (SD): 0.57) in the magnesium sulphate group, compared with 3.2 (SD: 0.98) in the control group.

Neonatal/infant

Badawy 2012 did not report on admission to neonatal intensive care unit or special care nursery for the infant.

Secondary outcomes

Maternal

The addition of magnesium sulphate to routine treatment, compared with routine treatment alone, was shown to significantly improve lung function, as measured by FEV1 (%) (MD 23.63%; 95% CI 19.72 to 27.54; 60 women) (Analysis 1.2); FVC (%) (MD 16.63%; 95% CI 10.44 to 22.82; 60 women) (Analysis 1.3); FEV1/FVC (%) (MD 19.42%; 95% CI 14.52 to 24.32; 60 women) (Analysis 1.4); FEV25% (MD 11.65%; 95% CI 8.06 to 15.24; 60 women) (Analysis 1.5); FEV75% (MD 12.92%; 95% CI 8.91 to 16.93; 60 women) (Analysis 1.6); and PEF (%) (MD 18.03%; 95% CI 12.49 to 23.57; 60 women) (Analysis 1.7).

There was no difference observed between groups in Badawy 2012 in the numbers of caesarean births (risk ratio (RR) 0.83; 95% CI 0.43 to 1.63; 60 women) (Analysis 1.8).

Badawy 2012 did not report on: asthmatic symptoms, asthma medication requirements, inflammatory markers, asthma self-management skills, quality of life, days/time lost from work/school, pregnancy-induced hypertension, pre-eclampsia/eclampsia, gestational diabetes, antepartum haemorrhage, postpartum haemorrhage, preterm prelabour ruptured membranes, preterm labour, chorioamnionitis, hyperemesis, adverse effects and discontinuation of the intervention due to adverse effects, or adherence with the intervention.

Fetal/neonatal

Badawy 2012 did not report on any of the secondary review outcomes for the fetus/neonate, however reported that both groups had a *"smooth neonatal period"*.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Badawy 2012 did not report on any of the outcomes for the fetus/neonate that were not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Badawy 2012 did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

Badawy 2012 did not report on any of the secondary review outcomes related to the use of health services.

2. Intravenous theophylline versus control (for acute asthma)

One trial involving 65 women was included in this comparison (Wendel 1996).

Primary outcomes

Maternal

Wendel 1996 did not report on asthma exacerbations.

Neonatal/infant

Wendel 1996 did not report on admission to neonatal intensive care unit or special care nursery for the infant.

Secondary outcomes

Maternal

In Wendel 1996, three of the 33 women admitted to hospital for an acute asthma exacerbation who received intravenous aminophylline (5 mg/kg loading dose, then 0.5 mg/kg maintenance) in addition to intravenous methylprednisolone 1 mg/kg every eight hours (maximum single dose 80 mg) discontinued the intervention due to adverse effects (nervousness, vomiting, or insomnia with therapeutic serum concentrations), compared with none of the 32 women who received intravenous methylprednisolone alone. This difference between groups was not statistically significant (RR 6.79; 95% CI 0.36 to 126.50; 65 women) (Analysis 2.1).

Wendel 1996 did not report on: asthmatic symptoms, asthma medication requirements, inflammatory markers, asthma self-management skills, quality of life, days/time lost from work/school, pregnancy-induced hypertension, pre-eclampsia/eclampsia, gestational diabetes, caesarean birth, antepartum haemorrhage, postpartum haemorrhage, preterm prelabour ruptured membranes, preterm labour, chorioamnionitis, hyperemesis, or adherence with the intervention.

Fetal/neonatal

There were no stillbirths or neonatal deaths reported in either group in the Wendel 1996 trial (Analysis 2.2; Analysis 2.3). Similary, no cases of preterm birth were reported (Analysis 2.4).

Wendel 1996 did not report on termination of pregnancy, gestational age at birth, birthweight, low birthweight and small-for-gestational age, Agpar score less than seven at five minutes, need for active resuscitation, jaundice, neonatal sepsis or congenital malformations.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Wendel 1996 did not report on any of the outcomes for the fetus/neonate that were not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Wendel 1996 did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

Wendel 1996 reported that there was no difference in the mean length of hospitalisation following an acute exacerbation between the aminophylline and usual treatment groups (theophylline group: 3.2 days; control group: 2.7 days) (standard deviations were not reported) (Analysis 2.5).

Wendel 1996 did not report on emergency department visits for the mother, admission to intensive care unit for the mother, length of postnatal hospitalisation for the mother, length of neonatal hospitalisation for the infant, or costs of care for the mother, baby or both.

3. Inhaled corticosteroid versus control

Three trials involving 374 women were included in this comparison (Caramez 1998; Silverman 2005; Wendel 1996), however for each outcome, only one or two of the trials contributed outcome data. We were able to perform meta-analyses for only two outcomes.

Primary outcomes

Maternal

There was no clear difference in the risk of asthma exacerbations for women who received inhaled beclomethasone in addition to usual treatment (an inhaled bronchodilator and oral corticosteroid taper), compared with those receiving usual treatment alone in the Wendel 1996 trial (RR 0.36; 95% confidence interval (CI) 0.13 to 1.05; 60 women) (P = 0.06) (Analysis 3.1).

The Caramez 1998 trial also reported on asthma exacerbations, comparing women who received inhaled beclomethasone in addition to routine asthma therapy with those receiving routine treatment only. The abstract reported that *"There was no statistic significant difference between the two asthmatic patients groups concerning number of asthma exacerbations (23/49 x 28/46 p=ns) and exacerbations during delivery (10/49 x 7/46, p=ns)."* As it could not be confidently determined from the information contained in the published abstract whether these results pertained to the total number of exacerbations, or numbers of women who experienced exacerbations, these data were not combined with data from the Wendel 1996 trial in a meta-analysis.

Neonatal/infant

The three trials included in this comparison did not report on admission to neonatal intensive care unit or special care nursery for the infant.

Secondary outcomes

Maternal

No difference was shown overall for the outcome caesarean birth when an inhaled corticosteroid (Caramez 1998: beclomethasone; Silverman 2005: budesonide) in addition to usual treatment was compared with usual treatment alone (average RR 1.65; 95% CI 0.57 to 4.79; two trials, 314 women) (Analysis 3.2). Substantial statistical heterogeneity was identified for this outcome ($T^2 = 0.44$; $I^2 = 71\%$), which is likely to be in part explained by the use of different corticosteroids, according to different regimens, and thus a random-effects model was used; the subgroup interaction test (comparing the two trials) was not significant ($Chi^2 = 3.06$, P = 0.08, $I^2 = 67.4\%$).

In the Wendel 1996 trial, full adherence with the intervention was reported (RR 1.00; 95% CI 0.94 to 1.07; 60 women) (Analysis 3.3); adherence was considered appropriate if the returned inhalers weighed 75% of the normative values.

The three trials did not report on: asthmatic symptoms, asthma medication requirements, lung function, inflammatory markers, asthma self-management skills, quality of life, days/time lost from work/school, pregnancy-induced hypertension, pre-eclampsia/eclampsia, gestational diabetes, antepartum haemorrhage, postpartum haemorrhage, preterm prelabour ruptured membranes, preterm labour, chorioamnionitis, hyperemesis, adverse effects and discontinuation of the intervention due to adverse effects.

Maternal (outcomes not pre-specified at protocol stage)

The Caramez 1998 trial reported on *"obstetric complications"*, and found no difference between the inhaled beclomethasone and usual treatment groups (RR 0.79; 95% CI 0.40 to 1.59; 95 women) (Analysis 3.12); and similarly, found no difference between groups for the outcome *"perinatal complications"* (RR 1.41; 95% CI 0.71 to 2.81; 95 infants) (Analysis 3.13).

Fetal/neonatal

There were no differences observed in the Silverman 2005 trial in the numbers of induced abortions (reasons not given) (RR 0.57; 95% CI 0.15 to 2.24; 219 women) (Analysis 3.4) and spontaneous abortions (RR 1.56; 95% CI 0.75 to 3.25; 219 women) (Analysis 3.5), between the inhaled budesonide and usual treatment groups. There were no perinatal deaths (stillbirths or neonatal deaths) in the Wendel 1996 trial (Analysis 3.6; Analysis 3.7).

Similarly, there were no differences observed between the inhaled corticosteroid and usual treatment groups for the outcomes preterm birth (RR 0.84; 95% CI 0.43 to 1.63; two trials, 314 women) (Analysis 3.8), birthweight (MD -34.00 g; 95% CI -290.17 to 222.17; one trial, 95 infants) (Analysis 3.9), Apgar score less than seven (timing not reported) (RR 0.94; 95% CI 0.06 to 14.57; one trial, 95 infants) (Analysis 3.10), or congenital malformations (not described) (RR 0.29; 95% CI 0.03 to 2.52; one trial, 219 infants) (Analysis 3.11).

The three trials did not report on: gestational age at birth, low birthweight, small-for-gestational age, need for active resuscitation, jaundice or neonatal sepsis.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

The three trials did not report on the fetal/neonatal outcomes that were not pre-specified at protocol stage, though Silverman 2005 reported on *"healthy children delivered"* and did not detect a difference between the inhaled budesonide and usual treatment groups (RR 0.99; 95% CI 0.86 to 1.15; 219 infants) (Analysis 3.14); and similarly reported no difference between groups for the outcome *"other adverse outcomes"* (RR 0.76; 95% CI 0.13 to 4.49; 219 infants) (Analysis 3.15).

Infant/child/adult (outcomes not pre-specified at protocol stage)

The three trials included in this comparison did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

The three trials did not report on any of the secondary review outcomes related to the use of health services.

4. Inhaled corticosteroid versus oral theophylline

One trial involving 398 women was included in this comparison (Dombrowski 2004).

Primary outcomes

Maternal

There was no difference observed between women receiving inhaled beclomethasone and women receiving oral theophylline in the occurrence of asthma exacerbations (RR 0.88; 95% CI 0.59 to 1.33; 385 women) (Analysis 4.1).

Neonatal/infant

Dombrowski 2004 did not report on admission to neonatal intensive care unit or special care nursery for the infant.

Secondary outcomes

Maternal

There were no differences seen in the occurrence of asthma symptoms at delivery (RR 1.09; 95% CI 0.71 to 1.68; 378 women) (Analysis 4.2), or the frequency of nocturnal asthma symptoms (MD -0.02; 95% CI -0.07 to 0.02; 385 women) (Analysis 4.3), between women receiving inhaled beclomethasone and women receiving oral theophylline.

Considering asthma medication requirements, there were no differences observed between the inhaled beclomethasone and oral theophylline groups in the use of rescue oral corticosteroids for exacerbations (RR 0.75; 95% CI 0.40 to 1.39; 385 women) (Analysis 4.4), or in the mean number of albuterol puffs per day (MD -0.10; 95% CI -0.54 to 0.34; 385 women) (Analysis 4.5). Similarly, considering lung function measures, there were no differences observed between groups in the proportion of study visits with FEV1 less than 80% predicted (MD -0.05; 95% CI -0.12 to 0.01; 385 women) (Analysis 4.6), or the proportion of study visits with PEFR less than 80% predicted (MD -0.04; 95% CI -0.09 to 0.02; 385 women) (Analysis 4.7).

No differences were detected between the inhaled beclomethasone and oral theophylline groups for the outcomes, pre-eclampsia (RR 1.04; 95% CI 0.53 to 2.05; 384 women) (Analysis 4.8), caesarean birth (RR 1.01; 95% CI 0.63 to 1.62; 384 women) (Analysis 4.9), postpartum haemorrhage (defined as blood loss of greater than 500 mL for vaginal births and greater than 1 L for caesarean births) (RR 1.17; 95% CI 0.52 to 2.65; 358 women) (Analysis 4.10), chorioamnionitis (RR 0.98; 95% CI 0.42 to 2.30; 384 women) (Analysis 4.11), adverse effects attributed to the intervention (including nausea (RR 0.33; 95% CI 0.11 to 1.00; 385 women), nervousness (RR 0.33; 95% CI 0.07 to 1.61; 385 women), insomnia (RR 0.09; 95% CI 0.00 to 1.61; 385 women), tremor (RR 0.25; 95% CI 0.03 to 2.18; 385 women), palpitations (RR 0.66; 95% CI 0.11 to 3.88; 385 women) and heartburn (RR 2.95; 95% CI 0.12 to 72.06; 385 women)) (Analysis 4.12). Women receiving inhaled beclomethasone were however significantly less likely to discontinue the intervention because of adverse effects, compared with women receiving oral theophylline (RR 0.35; 95% CI 0.14 to 0.86; 384 women) (Analysis 4.13); six women (3.1%) receiving inhaled beclomethasone ceased treatment because of adverse effects, compared with 17 women (8.9%) receiving oral theophylline.

No difference was observed between groups for self-reported adherence (MD 0.01; 95% CI -0.06 to 0.08; 385 women) (Analysis 4.14), however, women in the theophylline group had significantly higher measured adherence (assessed by serum theophylline concentrations, pill counts and weighing the used beclomethasone canisters) (MD -0.08; 95% CI -0.16 to -0.01; 322 women) (Analysis 4.15)).

Dombrowski 2004 did not report on inflammatory markers, asthma self-management skills, quality of life, days/time lost from work or school, pregnancy-induced hypertension, gestational diabetes, antepartum haemorrhage, preterm prelabour ruptured membranes, preterm labour or hyperemesis.

Fetal/neonatal

No differences were detected between the inhaled beclomethasone and oral theophylline groups for the outcomes perinatal death (reported as 'perinatal demise'; stillbirth and neonatal death were not reported separately) (RR 0.77; 95% CI 0.18 to 3.41; 374 infants) (Analysis 4.16), gestational age at birth (MD -0.10 weeks, 95% CI -0.83 to 0.63; 384 infants) (Analysis 4.17), preterm birth (RR 1.26; 95% CI 0.83 to 1.93; 384 infants) (Analysis 4.18), birthweight (MD 16.00 g; 95% CI -128.25 to 160.25; 384 infants) (Analysis 4.19), low birthweight (less than 2500 g) (RR 1.03; 95% CI 0.51 to 2.08; 310 infants) (Analysis 4.20), small-for-gestational age (RR 1.03; 95% CI 0.44 to 2.40; 310 infants) (Analysis 4.21), discharge diagnosis of sepsis (RR 0.70; 95% CI 0.22 to 2.15; 377 infants) (Analysis 4.22), or major congenital malformations (RR 1.18; 95% CI 0.36 to 3.79; 382 infants) (Analysis 4.23).

Dombrowski 2004 did not report on termination of pregnancy, Apgar score of less than seven at five minutes, need for active resuscitation, or jaundice.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Dombrowski 2004 did not report on any of the outcomes for the fetus/neonate that were not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Dombrowski 2004 did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

Considering the use of health services, no differences were observed between the inhaled beclomethasone and oral theophylline

groups for antenatal hospital admissions for the mother associated with an exacerbation (RR 0.66; 95% CI 0.30 to 1.42; 385 women) (Analysis 4.24) or emergency department visits for the mother associated with an exacerbation (RR 0.82; 95% CI 0.53 to 1.28; 385 women) (Analysis 4.25).

Dombrowski 2004 did not report on admission to the intensive care unit for the mother, postnatal hospitalisation for the mother, length of neonatal hospitalisation for the infant, or costs of care for the mother, baby or both.

5. FENO algorithm versus clinical guideline algorithm to adjust asthma therapy

Primary outcomes

One trial involving 220 women was included in this comparison (Powell 2011).

Maternal

The group of women who had their treatment (inhaled corticosteroid therapy) adjusted using a validated FENO-based treatment algorithm experienced significantly fewer asthma exacerbations compared with the group who had their treatment adjusted according to a clinical guideline-based algorithm (RR 0.61; 95% CI 0.41 to 0.90; 220 women) (Analysis 5.1); 28/111 (25.2%) women in the FENO group had an exacerbation, compared with 45/109 (41.3%) in the clinical guideline group.

Neonatal/infant

There was a trend towards fewer admissions to the neonatal intensive care unit or special care nursery for infants born to mothers who had their treatment adjusted using a validated FENO-based treatment algorithm, with eight admissions for the 105 infants in the FENO group, compared with 18 admissions for the 109 infants in the clinical guideline group (RR 0.46; 95% CI 0.21 to 1.02; 214 infants) (P = 0.05) (Analysis 5.2).

Secondary outcomes

Maternal

No clear significant differences were shown between the group of women who had their treatment adjusted using a validated FENO-based treatment algorithm compared with the group of women who had their treatment adjusted according to a clinical guideline-based algorithm for the outcomes: asthmatic symptoms (as assessed by ACQ score: MD -0.16; 95% CI -0.36 to 0.04; 220 women (Analysis 5.3); and symptom-free days per week (median (IQR) FENO algorithm group: 7 (4 to 7); clinical algorithm group: 6 (2 to 7); P = 0.058) (Analysis 5.4)); and lung function at the end of the study (as measured by FENO (ppb), FEV1 (L) and FEV1 (%) (Analysis 5.8)). Considering asthma medication requirements, the FENO-based treatment algorithm resulted in significantly more women being treated with inhaled corticosteroids at the end of the study, compared with the clinical guideline-based algorithm group (RR 1.62; 95% CI 1.26 to 2.09; 220 women) (Analysis 5.5). Similarly, more women received long-acting β-agonists in the FENO group than in the clinical guideline group (RR 2.33; 95% CI 1.46 to 3.71; 220 women) (Analysis 5.6), and short-acting β-agonist use was significantly less in the FENO group than in the clinical guideline group (Analysis 5.7). Though lower in the FENO group, the beclomethasone dipropionate equivalent inhaled corticosteroid dose did significantly differ between groups (Analysis 5.7).

Considering quality of life, women in the FENO group scored higher on the SF-12 mental summary (low = 0; high = 100) (median (IQR) FENO group: 56.9 (50.2 to 59.3); clinical guideline group: 54.2 (46.1 to 57.6); P = 0.037); however no difference between groups was shown for the SF12 physical summary score, or the Asthma Quality of Life Questionnaire - Marks (AQLQ-M) total score (Analysis 5.9).

No differences between groups were shown for the maternal outcomes, pregnancy-induced hypertension (RR 0.65; 95% CI 0.26 to 1.61; 210 women) (Analysis 5.10); pre-eclampsia (RR 0.61; 95% CI 0.15 to 2.49; 210 women) (Analysis 5.11); gestational diabetes (RR 0.74; 95% CI 0.31 to 1.77; 210 women) (Analysis 5.12); caesarean birth (elective: RR 0.83; 95% CI 0.42 to 1.63; 210 women; non-elective: RR 0.75; 95% CI 0.36 to 1.55; 210 women) (Analysis 5.13); antepartum haemorrhage (RR 1.02; 95% CI 0.06 to 16.08; 210 women) (Analysis 5.14); postpartum haemorrhage (RR 1.27; 95% CI 0.35 to 4.61; 210 women) (Analysis 5.15); ruptured membranes (RR 1.36; 95% CI 0.60 to 3.09; 210 women) (Analysis 5.16); or hyperemesis (no events in either group) (Analysis 5.17).

Powell 2011 did not report on inflammatory markers, asthma self-management skills, days/time lost from work or school, preterm labour, chorioamnionitis, adverse effects and discontinuation of the intervention due to adverse effects, and adherence with the intervention.

Fetal/neonatal

There was one termination in the FENO group (Analysis 5.18), and there was one stillbirth in each group (Analysis 5.19).

There was no significant difference between groups for gestational age at birth (weeks) (median (IQR) FENO group: 39.9 (38.7 to 40.7); clinical guideline group: 39.6 (38.4 to 40.6); P = 0.224) (Analysis 5.20); preterm birth (RR 0.69; 95% CI 0.26 to 1.88; 214 infants) (Analysis 5.21); birthweight (g) (median (IQR) FENO group: 3520 (3060 to 3920); clinical guideline group: 3460 (3040 to 3730); P = 0.233) (Analysis 5.22); low birthweight (< 2500

g) (RR 1.04; 95% CI 0.31 to 3.48; 214 infants) (Analysis 5.23); small-for-gestational age (RR 0.91; 95% CI 0.47 to 1.77; 214 infants) (Analysis 5.24); and jaundice (RR 1.04; 95% CI 0.21 to 5.03; 214 infants) (Analysis 5.25). There was one congenital malformation in the FENO group (Analysis 5.26).

Powell 2011 did not report on neonatal death, Apgar score of less than seven at five minutes, need for active resuscitation at birth, or neonatal sepsis.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Powell 2011 did not report on any of the outcomes for the fetus/neonate that were not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Infants born to mothers in the FENO group were less likely to have recurrent episodes of bronchiolitis in their first 12 months of life (Analysis 5.27) (RR 0.09; 95% CI 0.01 to 0.69; 128 infants); a trend towards fewer infants with recurrent episodes of croup in their first 12 months of life for infants born to mothers in the FENO group was also observed (RR 0.13; 95% CI 0.02 to 1.04; 129 infants) (P = 0.05) (Analysis 5.28).

Powell 2011 did not report on any other longer-term outcomes for the infant as a child or adult.

Use of health services

Powell 2011 did not report on any of the secondary review outcomes related to the use of health services.

6. Pharmacist-led multi-disciplinary approach to management of maternal asthma (MAMMA) versus standard care

One trial involving 60 women was included in this comparison (Lim 2012).

Primary outcomes

Maternal

Lim 2012 reported that there were no exacerbations in either the MAMMA or standard care groups (Analysis 6.1).

Neonatal/infant

There were three neonatal intensive care or special care admissions among the 29 infants born to mothers in the MAMMA group, and two admissions among the 29 infants born to mothers in the standard care group (RR 1.50; 95% CI 0.27 to 8.32; 58 infants) (Analysis 6.2)

Secondary outcomes

Maternal

In Lim 2012, ACQ scores were not significantly different between groups at three-month assessment (MD -0.17; 95% CI -0.54 to 0.20; 58 women); however at six-month assessment, the mean ACQ score of the intervention group (mean: 0.54, SD: 0.32) was significantly lower (better) than that of the control group (mean: 1.1, SD: 0.67) (MD -0.56; 95% CI -0.83 to -0.29; 58 women) (Analysis 6.3); this difference was considered 'clinically significant' by the trial authors. The ACQ score in the intervention group decreased by a mean of 0.46 (SD: 1.05) at three months and 0.89 (SD: 0.98) at six months. The control group had a mean decrease of 0.15 (SD: 0.63) at three months and 0.18 (SD: 0.73) at six months. The MD in ACQ scores between groups was -0.31 (95% CI -0.76 to 0.14; 58 women) at three months and -0.71 (95% CI -1.15 to -0.27; 58 women) at six months; the difference at six months was significant (Analysis 6.3). All women in the intervention group had an ACQ score less than 1.5 indicating adequately controlled asthma, compared with 20/29 (69%) in the standard care group (RR 1.44; 95% CI 1.12 to 1.84; 58 women) (Analysis 6.4); this difference between groups was significant.

No women in either group of the Lim 2012 trial required oral corticosteroid use (Analysis 6.5), nor required any asthma-related days off work (Analysis 6.6). There was no difference between the MAMMA and standard care groups for the outcomes: hypertension during pregnancy (RR 5.00; 95% CI 0.25 to 99.82; 58 women) (Analysis 6.7), gestational diabetes (RR 5.00; 95% CI 0.25 to 99.82; 58 women) (Analysis 6.8) and caesarean birth (RR 0.89; 95% CI 0.40 to 1.98; 58 women) (Analysis 6.9).

Lim 2012 did not report on: lung function, inflammatory markers, asthma self-management skills, quality of life, pre-eclampsia/eclampsia, antepartum haemorrhage, postpartum haemorrhage, preterm prelabour ruptured membranes, preterm labour, chorioamnionitis, hyperemesis, adverse effects and discontinuation of the intervention due to adverse effects, or adherence with the intervention.

Fetal/neonatal

There was no difference between the MAMMA and standard care groups for the outcomes: gestational age at birth (MD 0.00 weeks; 95% CI -1.21 to 1.21; 58 infants) (Analysis 6.10), preterm birth (RR 1.50; 95% CI 0.27 to 8.32; 58 infants) (Analysis 6.11), birthweight (MD 7.80 g -324.94 to 340.54; 58 infants) (Analysis 6.12), small-for-gestational age (RR 1.00; 95% CI 0.07 to 15.24; 58 infants) (Analysis 6.13), Apgar scores at one and five minutes (MD 0.70; 95% CI -0.04 to 1.44; 58 infants) (MD 0.30; 95% CI -0.07 to 0.67; 58 infants) (Analysis 6.14). There were no congenital malformations reported in the Lim 2012 trial (Analysis 6.15).

Lim 2012 did not report on termination of pregnancy, stillbirth, neonatal death, low birthweight, need for active resuscitation (as-

sisted ventilation via an endotracheal tube) at birth, jaundice, and neonatal sepsis.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Lim 2012 did not report on any of the outcomes for the fetus/neonate that were not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Lim 2012 did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

In Lim 2012, there were no asthma-related hospital admissions or emergency visits for women in either group after trial commencement (Analysis 6.16; Analysis 6.17).

Lim 2012 did not report on length of postnatal hospitalisation for the mother, length of neonatal hospitalisation for the infant, or costs of care for the mother, baby or both.

7. Progressive muscle relaxation (PMR) versus sham training

One trial involving 64 women was included in this comparison (Nickel 2006).

Primary outcomes

Maternal

Nickel 2006 did not report on asthma exacerbations.

Neonatal/infant

Nickel 2006 did not report on admission to neonatal intensive care unit or special care nursery for the infant.

Secondary outcomes

Maternal

PMR sessions compared with sham training sessions, significantly improved lung function measurements for pregnant women with bronchial asthma; final FEV1 (L) (MD 0.47; 95% CI 0.23 to 0.71; 64 women) (Analysis 7.1); final PEFR (L/minute) (MD 50.60; 95% CI 44.80 to 56.40; 64 women) (Analysis 7.2).

Women who received PMR sessions, compared with women who received sham training sessions, were more likely to score lower on two of five scales of the State-Trait Anger Expression Inventory; State-Anger (MD -3.90; 95% CI -5.64 to -2.16; 64 women) and Trait-Anger (MD -5.60; 95% CI -7.42 to -3.78; 64 women). No differences were observed between groups for Anger-In (MD -1.10; 95% CI -2.82 to 0.62; 64 women); Anger-Out (MD -2.00; 95% CI -4.55 to 0.55; 64 women); or Anger-Control (MD 0.50; 95% CI -1.75 to 2.75; 64 women) (Analysis 7.3).

Women who received PMR sessions were more likely to score higher on five of the eight domains of the SF-36; role physical (MD 7.00; 95% CI 3.88 to 10.12); vitality (MD 7.70; 95% CI 3.67 to 11.73); social functioning (MD 12.80; 95% CI 8.50 to 17.10); role emotional (MD 12.20; 95% CI 8.09 to 16.31); mental health (MD 6.10; 95% CI 1.84 to 10.36). Differences were not observed for: physical functioning (MD 1.50; 95% CI -1.23 to 4.23); bodily pain (MD 3.10; 95% CI -1.46 to 7.66); or general health perceptions (MD 4.30; 95% CI -0.24 to 8.84) (Analysis 7.4).

Nickel 2006 did not report on: asthmatic symptoms, asthma medication requirements, inflammatory markers, asthma self-management skills, quality of life, days/time lost from work/school, pregnancy-induced hypertension, pre-eclampsia/eclampsia, gestational diabetes, caesarean birth, antepartum haemorrhage, postpartum haemorrhage, preterm prelabour ruptured membranes, preterm labour, chorioamnionitis, hyperemesis, adverse effects and discontinuation of the intervention due to adverse effects, or adherence with the intervention.

Fetal/neonatal

Nickel 2006 did not report on any of the secondary review outcomes for the fetus/neonate.

Fetal/neonatal (outcomes not pre-specified at protocol stage)

Nickel 2006 did not report on any of the secondary review outcomes for the fetus/neonate not pre-specified at protocol stage.

Infant/child/adult (outcomes not pre-specified at protocol stage)

Nickel 2006 did not report on longer-term outcomes for the infant as a child or adult.

Use of health services

Nickel 2006 did not report on any of the secondary review outcomes related to the use of health services.

DISCUSSION

Summary of main results

This systematic review aimed to assess the effects of interventions (pharmacologic and non-pharmacologic, including self-management interventions) for managing women's asthma in pregnancy on maternal and fetal/infant outcomes. Eight trials (randomising 1181 women and their babies), at a moderate risk of bias overall, were eligible for inclusion, and were assessed under seven different comparisons in the review. Five of the trials assessed pharmacological agents, including inhaled magnesium sulphate (Badawy 2012) and intravenous theophylline (Wendel 1996) for women following acute asthma exacerbations; and inhaled corticosteroids (beclomethasone and budesonide) (Caramez 1998; Silverman 2005; Wendel 1996), including verus oral theophylline (Dombrowski 2004) for maintenance therapy. The other three trials assessed non-pharmacological interventions for asthma management during pregnancy, including a validated fractional exhaled nitric oxide (FENO)-based algorithm versus a clinical guideline-based algorithm to adjust asthma therapy (Powell 2011), a pharmacist-led multi-disciplinary approach to asthma management versus standard care (Lim 2012), and progressive muscle relaxation (PMR) versus sham training (Nickel 2006).

Considering primary review outcomes, relatively few differences were seen across the seven comparisons for the trials that reported on these outcomes. For women following acute asthma exacerbations, inhaled magnesium sulphate in addition to standard treatment in Badawy 2012 (60 women) was shown to significantly reduce the frequency of acute exacerbations before birth. The Badawy 2012 trial was however judged to be at an unclear risk of bias overall; thus this result must be interpreted with caution. In the Wendel 1996 trial (65 women), which assessed the addition of intravenous theophylline to standard treatment in acute asthma, asthma exacerbations were not reported. An inhaled corticosteroid (beclomethasone) in addition to usual treatment for maintenance therapy, did not have a clear effect on asthma exacerbations in two trials (of largely unclear methodological quality) (Caramez 1998; Wendel 1996) (155 women); and when inhaled beclomethasone was compared to oral theophylline in the Dombrowski 2004 trial for maintenance therapy (385 women), no clear difference was shown in the rate of exacerbations. None of the five trials assessing pharmacological interventions reported on the neonatal primary outcome of neonatal intensive care unit admissions.

In regards to non-pharmacological interventions, the use of a validated FENO-based treatment algorithm (compared with a clinical guideline-based algorithm) to adjust asthma therapy (FENO used to adjust dose of inhaled corticosteroids; and Asthma Control Questionnaire score used to adjust dose of long-acting β2 agonist) was shown to reduce exacerbations in Powell 2011 (220 women), and a trend towards reduced neonatal intensive care unit admissions was also shown. No women in Lim 2012 (60 women) (assessing a pharmacist-led multi-disciplinary approach to maternal asthma management) had exacerbations, and no difference was shown in the risk of admission to the neonatal intensive care unit in this trial. In Nickel 2006 (64 women), comparing PMR with sham training, asthma exacerbations and neonatal intensive care unit admissions were not reported.

Similarly, across the seven comparisons, there were few differences observed for secondary review outcomes. In the Wendel 1996 trial, intravenous theophylline in addition to usual treatment following acute exacerbations was not associated with differences in maternal or infant outcomes (discontinuation due to adverse effects, stillbirth, neonatal death, preterm birth, length of hospitalisation). The addition of inhaled magnesium sulphate compared to routine treatment following acute exacerbations in Badawy 2012, was however shown to improve lung function (as measured by FEV1, FVC, FEV1/FVC, FEF25-75 and PEF) compared to routine treatment alone. No difference was seen for caesarean birth (the only other outcome reported in the Badawy 2012 trial).

When inhaled corticosteroids in addition to usual treatment were compared with no additional treatment for maintenance therapy (Caramez 1998; Silverman 2005; Wendel 1996), no differences were seen for the secondary outcomes reported (including: caesarean birth, compliance with the intervention, abortion, stillbirth, neonatal death, preterm birth, birthweight, Agpar score less than seven, congenital malformations). When inhaled beclomethasone was compared with oral theophylline for maintenance therapy in one trial (Dombrowski 2004), no differences were seen for a range of maternal and infant outcomes (maternal: asthma symptoms, medication requirements, measures of lung function, pre-eclampsia, caesarean birth, postpartum haemorrhage, chorioamnionitis, self-reported compliancies) (infant: perinatal mortality, gestational age at birth, preterm birth, birthweight, low birthweight, small-for-gestational age, sepsis, major congenital malformations) (health services: antenatal hospital admissions, emergency department visits). While women receiving beclomethasone did not experience significantly fewer adverse effects overall (nausea, nervousness, insomnia, tremor, palpitations, heartburn), they were shown to have a significantly lower risk of discontinuing the intervention because of adverse effects, compared with women receiving oral theophylline (Dombrowski 2004).

In addition to significantly reducing asthma exacerbations, the FENO-based treatment algorithm in Powell 2011, was shown to improve some measures of quality of life (mental summary scores on the SF-12). The use of the FENO-based algorithm was also shown to influence treatment profile, with more women in this group receiving inhaled corticosteroids (though at a non-significantly lower equivalent dose) and long-acting β-agonists, and fewer women in this group receiving short-acting β-agonists. No differences were seen with the use of FENO-based management for the other maternal and infant outcomes reported by the trial (maternal: symptoms, lung function, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes, caesarean birth, antepartum or postpartum haemorrhage, ruptured membranes, hyperemesis) (infant: stillbirth, gestational age at birth, preterm birth, birthweight, low birthweight, small-for-gestational age, jaundice,

congenital malformations) (Powell 2011). At 12-month follow-up in Powell 2011, infants born to mothers in the FENO group were shown to have a significantly reduced risk of recurrent bronchiolitis, and a trend towards a reduced risk of recurrent croup.

When a pharmacist-led multi-disciplinary approach to management of maternal asthma was compared with standard care in Lim 2012, significant improvements in asthma control at six months were observed (which were not observed at three months). No other differences were seen in this trial for the maternal or infant secondary review outcomes that were reported (maternal: hypertension in pregnancy, gestational diabetes) (infant: gestational age at birth, preterm birth, birthweight, small-for-gestational age, Apgar scores, congenital malformations).

Finally, in Nickel 2006, when PMR was compared with sham training, improvements were seen in measures of lung function (FEV1 and PEFR) and in some measures of quality of life (five of eight domains on the SF-36 (role physical, vitality, social functioning, role emotional, mental health), and two of five scales on the State-Trait Anger Expression Inventory (State-Anger, Trait-Anger)).

The five trials in this review assessing pharmacological interventions did not provide clear evidence of benefits or harms to support or refute current practice (Badawy 2012; Caramez 1998; Dombrowski 2004; Silverman 2005; Wendel 1996), which varies, but commonly follows a 'step-wise approach', guided by randomised evidence from non-pregnant populations and observational data from pregnancy studies (Dombrowski 2008; NAEPP 2005; Schatz 2009). Short-acting bronchodilators (particularly short-acting inhaled β-agonists such as albuterol (salbutamol) have been recommended for symptom relief in women with mild, intermittent asthma; in mild persistent asthma, a daily low-dose inhaled corticosteroid has been recommended (with budesonide, with the greatest amount of safety data in pregnancy, preferred to beclomethasone, which was the inhaled corticosteroid assessed in three trials in this review (Caramez 1998; Dombrowski 2004; Wendel 1996)). Low-dose inhaled corticosteroids are favoured over methylxanthines, such as theophylline (which was the focus of two trials in this review (Dombrowski 2004; Wendel 1996)), mast cell stabilisers (such as cromolyn) and leukotriene-receptor antagonists. For moderate and severe persistent asthma, the combination of a low-dose inhaled corticosteroid with a long-acting β-agonist (such as salmeterol or formoterol) or an increased dose of the inhaled corticosteroid has been recommended. For the management of exacerbations during pregnancy, the use of a combination of pharmacological agents including short-acting inhaled β-agonists, inhaled anticholinergic agents (ipratropium bromide), and oral/intravenous systemic corticosteroids, has been supported (Dombrowski 2008; NAEPP 2005; Schatz 2009); the addition of inhaled magnesium sulphate for exacerbation management, which showed some benefits in one trial in this review (Badawy 2012), is not currently recommended in practice.

Three trials included in this review provide promise for the optimisation of asthma management in pregnancy with the use of non-pharmacological interventions (Lim 2012; Nickel 2006; Powell 2011). Though positive effects on asthma control were observed in this review with PMR (one trial: Nickel 2006), and a pharmacist-led, multi-disciplinary approach to management (with the provision of education and regular review) (one trial: Lim 2012), this evidence is unlikely to be sufficient to support clinical practice recommendations. Similarly, while the use of an algorithm incorporating FENO to adjust inhaled corticosteroid dose and asthma symptoms to adjust β-agonist dose showed reductions in exacerbations during pregnancy, and changes in maintenance pharmacologic therapy (with more frequent use of inhaled corticosteroids at lower daily doses), this evidence is unlikely to be sufficient to recommend universal implementation into the antenatal care setting (Powell 2011). The benefits and/or harms for perinatal outcomes are as yet, uncertain; further, there is a need to consider and evaluate the resource implications of such a management strategy, given that FENO measurement devices are not routinely available in many clinical settings. Though the randomised evidence for non-pharmacological interventions for asthma management in pregnancy accumulated to date is unlikely to be sufficient for widespread practice change, the need for such strategies to be incorporated into the management of a woman's asthma during pregnancy is increasingly being recognised. Clinical practice guidelines have highlighted the need to ensure that pregnant women have access to education about asthma and its relationship with pregnancy, and have the opportunity to develop the skills necessary for asthma management (such as correct inhaler technique, ability to self-monitor and follow a long-term management plan, and knowledge of how to promptly handle signs of worsening asthma) (Dombrowski 2008; NAEPP 2005).

Overall completeness and applicability of evidence

There is currently a lack of randomised evidence in this area, with only eight trials completed to date. The largest trial included almost 400 women (Dombrowski 2004), however, in five of the included trials, the sample sizes were of less than 100 women (Badawy 2012; Caramez 1998; Lim 2012; Nickel 2006; Wendel 1996)). Encouragingly, at least five further trials are currently planned or underway (ACTRN12613000202763; ACTRN12613000244707; ACTRN12613000301763; ACTRN12613000800729; NCT01345396).

The scarcity of data for the management of asthma during pregnancy was evident, not only in the limited number of completed trials, but also in the small number of outcomes evaluated in some of the included trials. Considering primary outcomes, only five of the eight included trials reported on asthma exacerbations (Badawy 2012; Caramez 1998; Dombrowski 2004; Lim 2012; Powell 2011), and only two trials reported on neonatal intensive care unit or special care nursery admissions (Lim 2012; Powell

2011). For the majority of outcomes, data were reported by less than half of the included trials; the most commonly reported secondary review outcomes were lung function, stillbirth, birthweight, congenital malformations (each reported by four trials), preterm birth and caesarean birth (both reported by five trials). Only one (Powell 2011) of the eight included trials completed to date has reported on follow-up outcomes of the infants (Powell 2011 has reported on the outcomes of bronchiolitis and croup).

Clinical heterogeneity of the data and also of the study designs (with a variety of different interventions and comparisons assessed across the eight trials), meant that very little data could be pooled in meta-analysis, making interpretation difficult. Different methods of measuring outcomes, such as lung function, and different outcome definitions across trials, such as for asthma exacerbations, also made comparisons between trials difficult. At present there is no commonly accepted definition for asthma exacerbations. A further drawback of definitions for exacerbations is that they are currently based on retrospective criteria; prospective criteria for the definition of asthma exacerbations, including in pregnancy, would be desirable.

Two of the eight included trials assessed xanthines for asthma management in pregnancy; intravenous aminophylline was assessed for acute asthma (Wendel 1996), and oral theophylline for maintenance treatment of asthma (Dombrowski 2004). These agents are, however, now infrequently used in clinical practice, particularly outside of the United States and developing world (Giles 2013), with the risk-benefit balance shown to be unfavourable (Nair 2012; Seddon 2006; Tee 2007). If oral theophylline is to be used in pregnancy, careful titration of the dose and regular monitoring to maintain the recommended serum theophylline concentration are required, due to the potential for serious toxicity from excessive dosing (NAEPP 2005).

Three included trials evaluating inhaled corticosteroids for maintenance treatment utilised beclomethasone (Caramez 1998; Dombrowski 2004; Wendel 1996). While inhaled corticosteroids are currently recognised as the preferred preventative medication for managing asthma in pregnancy, it is important to note that agents such as fluticasone and budesonide (as utilised in the later Silverman 2005 and Powell 2011 trials), rather than beclomethasone, have been regarded as 'preferred' inhaled corticosteroids for use in pregnancy, with the most gestational safety data for budesonide (George 2012; NAEPP 2005).

The Powell 2011 trial, which revealed benefits of a FENO-based algorithm to adjust asthma therapy, included only non-smoking pregnant women. As a proportion of pregnant women (including pregnant asthmatic women) continue to smoke during pregnancy, it is important that the effects of this intervention in the smoking pregnant population are assessed.

Quality of the evidence

Overall, the methodological quality of the studies included in this review was moderate, with two trials judged to be of low risk of bias (Lim 2012; Powell 2011), four trials judged to be at a moderate risk of bias (Dombrowski 2004; Nickel 2006; Silverman 2005; Wendel 1996), and two trials judged to be at an unclear risk of bias (Badawy 2012; Caramez 1998).

Considering trials assessing pharmacological interventions, both the Badawy 2012 and Caramez 1998 trials were judged to be of an unclear methodological quality overall; similarly, the methodological quality of Wendel 1996 was largely unclear, however the trial was judged to be at high risk of both performance bias and reporting bias. Dombrowski 2004 and Silverman 2005 were judged to be at a comparatively higher quality (based on the available information) than the other pharmacological trials, with low risk of selection, performance, and detection bias; however the risks of attrition and reporting bias in these trials were unclear.

In regards to trials of non-pharmacological interventions, both Lim 2012 and Powell 2011 were judged to be of high methodological quality overall, with both trials judged to be at a low risk of selection, detection, attrition and reporting bias. Lim 2012 was however at an high risk of performance bias, due to the nature of the intervention, and the inability to blind participants and study personnel. The methodological quality of Nickel 2006 was less certain, as while methods for random sequence generation and blinding of outcome assessors were judged as adequate, the risks of selection bias (due to inadequate allocation concealment), and of performance, attrition and reporting bias, were unclear.

Potential biases in the review process

The search for studies in this area was performed using the Cochrane Pregnancy and Childbirth Group's Trials Register (which is updated weekly to monthly with information from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, handsearches from 30 journals and conference proceeding of major conferences and alerts for a further 44 journals) and using the Cochrane Airways Group's Trials Register (also updated weekly to monthly with information from CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, AMED, and handsearches from the proceedings of eight major conferences). It is unlikely that studies that have been conducted have been missed, however unpublished studies, or ongoing studies not registered in clinical trial registries could be missing. Should such studies be identified, we will include them in future updates of the review.

We aimed to reduce bias wherever possible by having at least two review authors independently working on study selection, data extraction and 'Risk of bias' assessment.

Agreements and disagreements with other studies or reviews

This systematic review is the first Cochrane review to assess the randomised controlled trial evidence of both pharmacological and non-pharmacological interventions for managing asthma during pregnancy.

In relation to non-pharmacological interventions, our findings are consistent with a recently published review of randomised trials of healthcare interventions for improving asthma in pregnant women (Zairina 2014). This review similarly concluded that while non-pharmacological interventions were associated some significant improvements in maternal asthma control and neonatal outcomes, that firm conclusions could not be drawn, due to the limited number of reported studies, the clinical heterogeneity of the interventions, variations in outcome measures and limitations in study designs (Zairina 2014).

While a Cochrane review of tailoring asthma interventions based on FENO (in comparison to clinical symptoms) in children and adults did not show clear benefits to recommend the use of FENO for clinical practice (Petsky 2009), the findings of the Powell 2011 trial, provide some promise for the use of a FENO-based algorithm to adjust asthma therapy in pregnant women. In contrast to the findings of the Petsky 2009 review, which showed that FENO did not significantly reduce exacerbations, and may be associated with higher doses of inhaled corticosteroids in children and adolescents, in Powell 2011, exacerbations for pregnant women were reduced with the use of FENO to adjust inhaled corticosteroid dose, and while more women in the FENO group were treated with inhaled corticosteroids, their mean daily dose was in fact lower (though not significant).

In Lim 2012 and Powell 2011, women were also provided with education on asthma self-management skills (inhaler technique, knowledge and action plans) and adherence was assessed and optimised. For Lim 2012, asthma education, monitoring, feedback and follow-up were integral components of the monthly intervention, and asthma action plans were recommended by the trial pharmacist, drafted alongside a respiratory physician and signed off by a family physician. Asthma education programs and self-management plans that enable individuals to adjust therapy based on written action plans have been proven to be effective in improving health outcomes in the general asthmatic population in randomised trials and systematic reviews (Gibson 2002); observational studies have also suggested benefits of asthma eduction and self-management skill development for pregnant women (Murphy 2005a). Previous studies have supported the utility of pharmacist-led or community pharmacy-based programs in asthmatic patients (Basheti 2007; Mehuys 2008), as was shown to be of potential benefit for pregnant women in Lim 2012; this topic will be the focus of an upcoming Cochrane review of pharmacy programs for all patients (Ryan 2013).

The use of relaxation therapies in the general asthmatic populations was the focus of a systematic review by Huntley 2002. In this review, five of the 15 included trials assessed PMR (as was the focus of the Nickel 2006 trial included in this review), and the authors concluded that while there is currently a lack of evidence for the efficacy of relaxation therapies in asthma management, largely due to the poor methodology of the studies, and inherent problems of conducting such trials, there is some evidence that muscular relaxation can improve lung function of patients with asthma (Huntley 2002); similar to the findings of the Nickel 2006 trial.

While many reviews in non-pregnant populations have strongly supported the use of inhaled corticosteroids such as inhaled beclomethasone (Adams 2005) and budesonide (Adams 1999), the benefits and potential harms for pregnant women have been less certain. Our review findings are in line with those of a recent, comprehensive systematic review of the safety of regular preventive asthma medications during pregnancy (Lim 2011b). This review similarly highlighted the lack of randomised evidence in this area, however concluded that while some negative outcomes of preventive asthma medications have been reported, that no clear, direct association with medication use in most of these cases has been shown. In this review, the use of inhaled corticosteroids was not shown to be associated with any particular adverse event (Lim 2011b).

When inhaled corticosteroids have been compared with oral xanthines (such as theophylline) in previous reviews, such as in children, it has been shown that while xanthines are an effective preventative treatment, they may be less effective than inhaled corticosteroids, with a less favourable side-effect profile (Seddon 2006). In this review, while the Dombrowski 2004 trial did not show oral theophylline to be less effective than inhaled beclomethasone, a higher rate of discontinuation due to adverse effects with oral theophylline was seen.

In regards to the use of inhaled magnesium sulphate in addition to routine treatment in the management of acute asthma, a recent Cochrane review (Powell 2011) did not show a significant improvement in lung function overall, as was suggested for pregnant women in the Badawy 2012 trial. This review, however acknowledged the considerable between-study heterogeneity, and noted that individual results from three of the included trials showed possible improvements in lung function with inhaled magnesium sulphate in those with severe asthma exacerbations (Powell 2012). The Badawy 2012 trial, however, was judged to be at an unclear risk of bias overall, with a lack of methodological information provided to confidently assess trial quality; thus the results of this trial should be interpreted with caution.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently a limited and incomplete body of evidence from randomised trials assessing the effects of interventions for managing asthma during pregnancy, which is insufficient to make firm

conclusions about optimal interventions. The ability to draw conclusions is limited particularly by variability in the quality of the trials conducted to date, by the small sample sizes of many of these trials, and by variation in characteristics of the interventions assessed in the trials.

The results from five trials in this review assessing pharmacological interventions did not provide clear evidence of benefits or harms to support or refute current practice (Badawy 2012; Caramez 1998; Dombrowski 2004; Silverman 2005; Wendel 1996). While inhaled magnesium sulphate was shown to reduce asthma exacerbations for pregnant women with acute asthma, this was in one small trial, of unclear quality (Badawy 2012), and thus this evidence is insufficient to guide practice. While no clear effect on asthma exacerbations was seen with the addition of inhaled beclomethasone to routine asthma therapy in two trials (Caramez 1998; Wendel 1996), these trials were also both of unclear methodological quality, and had small sample sizes.

Similarly, the randomised evidence for non-pharmacological interventions for asthma management in pregnancy accumulated to date is not sufficient to support widespread implementation or practice change. The three included trials provided some support for the use of such strategies, however were not powered to detect differences in important maternal and infant outcomes (Lim 2012; Nickel 2006; Powell 2011). While a FENO-based algorithm to adjust asthma therapy reduced exacerbations for pregnant women, the effects on perinatal outcomes were less certain, and thus widespread implementation into the clinical practice setting is not yet likely to be appropriate (Powell 2011). Similarly, though positive effects on asthma control were shown with PMR (Nickel 2006) and a pharmacist-led, multi-disciplinary approach to asthma management for pregnant women (Lim 2012), the evidence to date is insufficient to guide practice change.

Implications for research

In light of the limited current evidence, further randomised controlled trials are required to determine the most effective and safe management interventions for women with asthma during pregnancy. Future trials must be sufficiently powered, and well-designed, to allow important differences in relevant clinical outcomes for the mother and her baby to be detected, and to allow longer-term infant, child and/or adult outcomes to be assessed. The impact on health services of management interventions requires evaluation prior to implementation into clinical practice.

A number of important questions remain surrounding the optimal care of asthmatic pregnant women. If further trials are conducted focused on the effectiveness and safety of pharmacological agents, it is important that the agents assessed are either those commonly utilised or recommended in current clinical practice (for example, considering inhaled corticosteroids, budesonide, rather than beclomethasone, should be utilised in any planned trials), or novel agents, not yet assessed in pregnancy. In addition to evaluating effectiveness and safety, such trials may address specific considerations such as dosage.

Though future trials of pharmacological agents for asthma management in pregnancy are warranted, it is likely that research efforts will be primarily directed towards trials aimed at optimising asthma management through non-pharmacological interventions; there are a multitude of possible non-pharmacological strategies and combinations of strategies that may be assessed (as detailed in the Background of this review, non-pharmacologic strategies may include: monitoring lung function to guide treatment (such as the use of spirometry); monitoring of airway inflammation to guide treatment (such as the use of FENO); lifestyle modification and the avoidance of triggers (such as smoking cessation); dietary interventions; physical interventions; psychological interventions; educational programs and asthma action plans).

Given the benefits of a FENO-based algorithm to adjust asthma therapy observed in the Powell 2011 trial, further trials utilising an algorithm incorporating FENO to adjust inhaled corticosteroid therapy are a priority. At least one such trial (The Breathing for Life Trial: ACTRN12613000202763) is planned/underway in Australia, with a target size of over 1100 women; thus powered to detect a difference in a primary composite adverse outcome for the infant (preterm birth, intrauterine growth restriction, perinatal mortality or neonatal hospitalisation at birth). Importantly, the trial aims to assess this management strategy in both smoking and non-smoking pregnant women (non-smoking women alone were the focus of the Powell 2011 trial). Further trials of interventions that have shown promise, such as the use of PMR (Nickel 2006), and a pharmacist-led, multi-disciplinary approach to management (Lim 2012), powered to detect differences in asthma exacerbations and perinatal outcomes are needed; the cost-effectiveness of these interventions should also be evaluated.

Four additional randomised trials have been identified as being planned or underway (see: Ongoing studies), three in Australia (ACTRN12613000244707; ACTRN12613000301763; ACTRN12613000800729) and one in Belgium (NCT01345396). One trial (target sample size: 378 women) aims to assess a respiratory nurse-led 'Antenatal Asthma Management Service' (AAMS) based in the antenatal outpatient clinic compared with standard care (ACTRN12613000244707); one trial (target sample size: 104 women) aims to assess dietary modification for asthma control (increased consumption of antioxidant rich foods) (ACTRN12613000301763); one trial (target sample size: 70 women), 'Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy' (MASTERY) aims to assess the effects of a 'Breathe-easy' mobile phone application (ACTRN12613000800729); and the final trial (target sample size: 80 women) aims to assess the effects of an asthma education program on asthma control (NCT01345396).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Badawy 2012

Methods	Randomised controlled trial.
Participants	60 women were randomised. **Setting:** Sohag University Hospital, Eqypt from October 2010 to June 2011 **Inclusion criteria:** pregnant women who were not completely or partially controlled on routine acute asthma therapy; with a history of bronchial asthma under routine therapy; with clinical evaluation of bronchial asthma according to GINA guidelines **Exclusion criteria:** women with the following complications: congestive heart failure, angina history, renal problems, history suggestive of pulmonary embolism; women with very severe asthma presenting with manifestations requiring endotracheal intubation; associated medical illness from history/medical examination (diabetes, hypertension); fever of more than 38 degrees; inability to perform pulmonary function test
Interventions	**Intervention group (inhaled magnesium sulphate) (n = 30)** Women received routine treatment for acute asthma exacerbations, which include oxygen, intravenous corticosteroids (solucortif 100 mg vial), intravenous aminophylline (500 mg/5 mL), and nebulised salbutamol and magnesium sulphate (mixture of: 1 mL salbutamol, 1 mL (500 mg) magnesium sulphate, and 8 mL normal saline) **Control group (n = 30)** Women received routine treatment for acute asthma exacerbations, as above (including nebulised salbutamol (1 mL salbutamol solution dissolved in 9 mL normal saline, with no magnesium sulphate) Women received a maximum of 3 sets of nebulisation, 20 minutes apart; 2 hours later, pulmonary function tests and blood gas analysis were done All women were allowed to be discharged from the emergency unit when their signs of distress and dyspnoea were improved; their oxygen saturation was more than 94%; and their FEV1 was more than 60%. If women did not meet these signs of improvement they were admitted to the intensive care unit for monitoring and management; women were then followed up in the outpatient clinic with routine antenatal care
Outcomes	Pulse rate; pH; arterial oxygen tension; arterial carbon dioxide tension; oxygen saturation; potassium; FEV1; FVC; FEV1/FVC; FEF25%; FEF75%; PEFR; acute asthma exacerbations (until birth); mode of birth (normal vaginal birth; caesarean section); *"smooth neonatal period".*
Notes	Review authors have contacted trial authors for further information with no response as at 28/08/2014

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Badawy 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote from abstract *"Patients were divided into two groups in a double blind randomization."* Quote from manuscript: *"The studied patients were randomized into two groups through separate envelopes".*
Allocation concealment (selection bias)	Unclear risk	As above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:*"The medications were given by doctor who was not a part of the study..."*. Group A (control group) received routine treatment for acute exacerbations which included nebulised salbutamol (1 mL in 9 mL saline). Group B (intervention group) received the same treatment, however received nebulised salbutamol and magnesium sulphate (1 mL salbutamol, 1 mL magnesium sulphate, and 8 mL saline)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported for the 60 women.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine reporting bias.
Other bias	Unclear risk	Groups were comparable at baseline for reported characteristics (age, education, parity and duration of pregnancy). Insufficient information to determine other sources of bias

Caramez 1998

Methods	Randomised controlled trial.
Participants	95 women were randomised. **Setting:** Brazil. **Inclusion criteria:** pregnant asthmatic women. **Exclusion criteria:** none detailed.
Interventions	**Intervention group (inhaled beclomethasone) (n = 49)** Inhaled beclomethasone (1 mg/day); inhaled bronchodilators and tapered oral prednisolone during exacerbations **Comparison group (n = 46)** Inhaled bronchodilators and tapered oral prednisolone during exacerbations
Outcomes	Asthma exacerbations in pregnancy and during delivery; type of birth; obstetric complications; perinatal outcomes

Caramez 1998 (*Continued*)

Notes	Information taken from abstract only. Review authors have contacted trial authors for further information with no response as at 28/08/2014

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quotes: "*prospective, randomised, controlled study*"… *"randomly assigned";* with no further details (only abstract available).
Allocation concealment (selection bias)	Unclear risk	As above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in abstract.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine attrition bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine reporting bias.
Other bias	Unclear risk	Insufficient information to determine other risk of bias.

Dombrowski 2004

Methods	Randomised controlled trial.
Participants	398 women randomised (385 included in analyses). **Setting:** 13 centres of the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development, USA, from December 1995 to February 2000 **Inclusion criteria:** moderate asthma (see notes below for definition); singleton viable pregnancy and no major anomalies; < 26 weeks' gestation **Exclusion criteria:** prenatal care or birth planned elsewhere; imminent birth; gestational hypertension or pre-eclampsia; current (or history of) epilepsy treated with medications; allergy/sensitivity to theophylline; inhaled steroid or albuterol; treatment with oral corticosteroids for another medical condition; participation in another asthma study; active pulmonary disease other than asthma; cardiac disease; pre-gestational diabetes; endocrine disorders requiring medication; sickle cell disease; acute/chronic liver disease; inability to schedule an ultrasound; inability to give informed consent; women with unstable/severe asthma

Interventions	**Intervention group - inhaled beclomethasone (n = 199 randomised, 194 included in analyses)** Women received inhaled beclomethasone 4 puffs 3 times per day (504 mcg/d approximately), and placebo pills (assumed at the same regimen as the theophylline pills) **Comparison group - oral theophylline (n = 199 randomised, 191 included in analyses)** Women received inhaled placebo 4 puffs 3 times per day and theophylline pills - the initial dose was 200 mg morning and evening; this was increased to 300 mg 2 times per day after 3 days. The total dose was adjusted between 400-800 mg per day with a serum, target level of 8 to 12 mcg/mL **All women:** on randomisation all women were instructed to discontinue all other asthma medications and were supplied with open-label albuterol inhalers to be used on an 'as needed' basis. Women received spacers with the inhalers to reduce oral deposition and systemic absorption of the active drug. Dosage of placebo and theophylline tablets was halved during use of a macrolide antibiotic National Asthma Education and Prevention Program guidelines for asthma management constituted standard care (objective measures of pulmonary function, mitigating asthma triggers, patient education). Women were supplied with peak flow meters, asthma diaries, and plastic pillow and mattress covers. They were instructed in home environmental control measures, and in home rescue algorithms
Outcomes	**Primary outcome:** proportion of women with at least 1 validated asthma exacerbation (defined as asthma symptoms (cough, dyspnoea or wheezing) that resulted in a medical intervention, including an emergency visit, need for oral corticosteroids or hospitalisation) **Secondary** Treatment failure (see notes below for definition); withdrawal; other asthma outcomes (proportion study visits with FEV1 < 80%, or PEFR < 80% predicted; albuterol (mean daily puffs); nocturnal symptoms; symptoms at delivery); delivery and perinatal outcomes (chorioamnionitis; pre-eclampsia; preterm birth; haemorrhage; caesarean birth; oligohydramnios; gestational age at birth; birthweight; birth length; major malformation; perinatal demise; jitteriness; hyaline membrane disease; discharge diagnosis of sepsis)
Notes	**Moderate asthma:** women were considered to have moderate asthma if they had symptoms 8 or more days over the past 4 weeks not attributable to upper respiratory infections and/or a FEV1 60% to 80% predicted more than 4 hours after bronchodilator. Women with mild asthma by symptoms and FEV1, but who required regular medications for asthma control were also considered to have moderate asthma (with regular medication defined as at least 4 weeks of daily theophylline ($\geq$ 1 dose/day), ipratropium ($\geq$ 4 puffs/day), or 2 or more puffs per day of inhaled β2-agonists, cromolyn, nedocromil, or inhaled corticosteroids **Treatment failure:** defined as more than 2 asthma exacerbations resulting in an emergency visit/course of systemic corticosteroids, or 1 or more asthma hospitalisation $\geq$ 48 hours, or unacceptable symptoms. All treatment failures were considered to have achieved the primary outcome of the trial
Risk of bias	***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence, stratified by centre, was generated by the Biostatistics Coordinating Centre of George Washington University by using the simple urn model
Allocation concealment (selection bias)	Low risk	Study medications were packaged and labelled with a drug code by a central pharmacy that was responsible for distribution of study drugs to the centre. Each woman was randomly assigned by clinical centre staff by assigning the next sequentially numbered drug code and the corresponding study medication kit
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as 'double masked', with the use of placebos (inhaler/tablets). All investigators were blinded to the 3 interim analyses of data until completion of the study. Serum theophylline concentrations were obtained (samples taken from women in both groups), and the Biostatistics Co-ordinating Centre provided investigators with instructions to increase/decrease dose of theophylline pills; to maintain blinding, they also 'adjusted' the dose of placebo pills
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	398 women were randomised (199 to each group); only 13 (3.3%) women were lost to follow-up before primary outcome determination (these were excluded from all analyses). It is unclear for some outcomes how many women are lost, as the tables describe *"some data based on fewer than 385 participants"* but it is not clear for which outcomes, and for which groups. 1 woman in the theophylline group had primary outcome data, but delivery data could not be obtained. In regards to study completion and compliance data: *"Some data were lost by the service contracted to ascertain measured compliance; the remaining data are based on 132 women in the theophylline and 190 in the beclomethasone"* groups.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol, it is difficult to assess selective reporting (and secondary outcomes were roughly defined in the manuscript methods; quote: *"Secondary outcomes included treatment failures, participant withdrawal, and delivery and perinatal outcomes"*).

Dombrowski 2004 (*Continued*)

Other bias	Unclear risk	The frequency of self-reported smoking was significantly higher in the theophylline group. After an interim data review, it became evident that the aggregate frequency of the primary outcome would be below the projected 35%. To increase the primary outcome rate, the data safety and monitoring committee changed eligibility requirements after enrolment of 311 women to include only women who required regular asthma medications as they had a greater frequency of the primary outcome. 58 women in the beclomethasone group discontinued intervention, and 68 in the theophylline group discontinued the intervention (treatment failure, side effects, self-withdrawal)

Lim 2012

Methods	Randomised controlled trial.
Participants	60 women were randomised. **Setting:** antenatal clinics at 2 major Victorian women's hospitals, Australia **Inclusion criteria:** pregnant women with asthma attending antenatal outpatient clinics, up to 20 weeks' gestation, who could communicate in English **Exclusion criteria:** women under the age of 18 years; women who have not had asthma symptoms (wheeze, chest tightness, and/or use of reliever medication) in the last year; women unable to meet the demands of the trial; women included in a previous exploratory study 'Asthma during pregnancy; the experiences, concerns and views of pregnant women;' women who have a miscarriage or termination
Interventions	**Intervention group - Multi-disciplinary Approach to Management of Maternal Asthma (MAMMA©) (n = 30)** Women experienced a collaborative approach to asthma management - involving family, physicians, pharmacists and asthma educators. Asthma education, monitoring, feedback and follow-up were integral components of the monthly intervention. Women received pharmacist-led medication management review at the beginning of the trial, periodic review of inhaler device technique by asthma educator, trigger avoidance and smoking cessation support (if relevant). Each participant was given a hand-held, portable, electronic spirometer to encourage home-monitoring, and trained in how to use it. Women were instructed to contact the pharmacist if their lung function deteriorated (FEV1/FEV6 < 0.75). Each month participants were contacted by the trial pharmacist by phone/in person to assess their asthma control using a short data collection form which included the ACQ; assessments were approximately 30 minutes.The pharmacist provided feedback to the family physicians where the ACQ scores increased by 0.5 or more or if there had been documented exacerbations. The pharmacist and physician then collaborated on appropriate 'step-up' therapy for the women. Asthma action plans were also recommended by the trial pharmacist, and were drafted alongside a respiratory physician at the discretion of the woman's family physician who signed off on the final plan **Control group - standard care (n = 30)** Women received usual medical care (including regular antenatal visits) and did not

	receive the intervention, any additional monitoring or education sessions. If at follow-up (at 3 and 6 months) their asthma control was of concern (2 or more documented exacerbations without resolution since prior assessment, or their ACQ score was greater than 2, women were advised to notify their family physician) **Both groups of women** were given a summarised version of the 'Asthma and Healthy Pregnancy' brochure from the Asthma Foundation of New South Wales, Australia to minimise the risks of poorly controlled asthma
Outcomes	**Primary outcome:** ACQ score (change from baseline at 3 and 6 months). **Secondary outcomes:** asthma exacerbations (defined as having asthma-related hospital visits, emergency visits, days off work or oral corticosteroid use); development of antenatal complications (hypertensive disorders or pregnancy; antepartum haemorrhage; gestational diabetes; gestational age at birth); neonatal outcomes (gestational age at birth; birthweight percentile; Apgar scores; admission to neonatal intensive care or special care nursery; mode of birth; postnatal complications)
Notes	Pilot study.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence of numbers generated during the 'Random allocation' software program by an external researcher, not part of the research team
Allocation concealment (selection bias)	Low risk	Block randomisation (with stratification: mild intermittent asthma vs. moderate-severe persistent asthma) using random blocks of 4 and 6, using numbered, sealed opaque envelopes. The leading investigator allocated women to the usual care group or the intervention group at the time of recruitment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind women and study personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A research assistant, blinded to group allocation performed assessment at 3 and 6 months
Incomplete outcome data (attrition bias) All outcomes	Low risk	One woman from each group (2/60) withdrew from the trial. Intention-to-treat analysis performed
Selective reporting (reporting bias)	Low risk	No selective reporting identified; data reporting for all outcomes specified in the trial protocol
Other bias	Low risk	No other obvious risk of bias identified.

Nickel 2006

Methods	Randomised controlled trial.
Participants	64 women were randomised. **Setting:** Germany. **Inclusion criteria:** pregnant women suffering from bronchial asthma, who were regularly seen by a gynaecologist **Exclusion criteria:** women were excluded who had current use of medication, anything other than the usual types of asthma medication during the previous 4 weeks; psychosis; severe anxiety and/or depression; substance abuse; use of psychotropic medication or psychotherapy; or if they smoked or had hypertension
Interventions	**Intervention group - progressive muscle relaxation (PMR) (n = 32)** Women were treated in 30 minute group PMR sessions, 3 times per week over 8 weeks. Women deliberately applied tension to certain muscle groups then released the tension and focused on how the muscles relaxed during the process (right foot, right lower leg and foot, entire right leg, left foot, left lower leg and foot, entire left leg, right hand, right forearm and hand, entire right arm, left hand, left forearm and hand, entire left arm, abdomen, chest, neck and shoulders, face). The women received precise instructions for daily practice at home (15 minutes 2 times a day using shortened form of the procedure) **Control group - sham training (n = 32)** Women were prescribed movement with their extremities as a placebo intervention, also in 30-minute sessions 3 times a week. The women also received instruction for daily practice at home, using shortened exercises **Both groups** were tested weekly. All women were tested in the morning, under controlled room temperature and light conditions. Women were asked to not eat or drink and to abstain from sport, alcohol and caffeine during the 24 hours prior
Outcomes	Systolic blood pressure; FEV1; PEFR; heart frequency; coefficient of variation; high frequency; low frequency; middle frequency; State-Trait Anger Expression Inventory (STAXI) and Health Survey (SF-36) measures
Notes	All women participated in the PMR or sham training and were tested in the morning (8/9 am) under controlled room temperature and light conditions. Women were instructed not to eat or drink (only water allowed) and to abstain from sport, alcohol and caffeine during the 24 hours preceding the experiment

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "*Randomized numbers generate by an Excel table*".
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described in sufficient detail; quote: "*The clinic administration conducted the randomization procedure confidentially*".

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Sham training was used, although it is unclear whether this was effective in blinding women (i.e. the exercises/ instructions would have differed), and study personnel administering the training would have been aware of group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All measurements (blood pressure and lung parameter measurement, and ECG recordings) were arranged by blinded medical/technical personnel. Blinded professional staff checked the data for completeness (questionnaires). The data were twice fed independently to the computer and automatically checked for deviations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 women (2 in PMR group and 4 in control group) did not attend more than 2 examination days and *"dropped out of the study"*; however they were included in analyses (intention to treat), although it is unclear where the data from the lost women has come from
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting. No clinical outcomes related to pregnancy/birth were included
Other bias	Low risk	No other obvious risk of bias identified. Baseline characteristics were similar between groups

Powell 2011

Methods	Randomised controlled trial.
Participants	220 women randomised. **Setting:** 2 antenatal clinics (John Hunter Hospital and Maitland Hospital, New South Wales, Australia) from June 2007 to December 2010 **Inclusion criteria:** non-smoking pregnant women (> 18 years) with asthma attending the antenatal clinics; between 12 to 20 weeks' gestation; doctor's diagnosis of asthma; using inhaled therapy for asthma within the past year. Asthma diagnosis confirmed by respiratory physician's diagnostic interview **Exclusion criteria:** inability to attend antenatal clinic visits during pregnancy; inability to perform manoeuvres required for spirometry and FENO; requirement for > 3 courses of oral corticosteroid in the previous 12 months; admission to hospital for asthma exacerbation in the previous 3 months; maintenance oral corticosteroids; maintenance oral theophylline; current smoking; concomitant chronic medical illness; chronic lung disease; drug/alcohol dependence
Interventions	**All women:** FENO and spirometry were measured at visit 1 and ACQ administered. Asthma self-medication skills (inhaler technique, knowledge, action plan) and adherence were assessed and optimised. Eligible women commenced a 2 week 'run-in' period. Women using inhaled corticosteroids continued with their current dose (administered as

	budesonide with dose equivalence from guidelines); women with uncontrolled asthma, not using maintenance inhaled corticosteroids were started on budesonide. Following randomisation, women were reviewed monthly at the antenatal clinical until birth; a research assistant collected data for clinical symptoms, ACQ score, present treatment FENO and FEV1. ACQ score, treatment and FENO were sent to the algorithm keeper, who applied the relevant algorithm and sent the treatment recommendation to the research assistant in the clinic who informed the woman. Women were seen by the investigator in the clinic if their asthma was uncontrolled and they were at the maximum treatment level of the algorithm **Intervention group - FENO algorithm to adjust therapy (n = 111)** Asthma therapy (inhaled corticosteroid (budesonide) and long-acting β-agonist therapy (salbutamol/formoterol)) adjusted according to FENO during the 2nd and 3rd trimester of pregnancy (approximately 6 months). The FENO algorithm used a sequential process: first, the FENO concentration was used to adjust the dose of inhaled corticosteroids; and second, the ACQ score was used to adjust the dose of long-acting β2 agonist (see Additional Table 1 and Table 2). The cut-off points for the algorithm were derived from a prospective cohort study of asthma in pregnancy **Control group - clinical guideline algorithm to adjust therapy (n = 109)** Asthma therapy (inhaled corticosteroid and long-acting β-agonist therapy) adjusted according to clinical guidelines (GINA) during the 2nd and 3rd trimester of pregnancy (approximately 6 months). The clinical algorithm was based on asthma control (ACQ) with cut-off points defined as: well controlled asthma (< .75), partially controlled asthma (0.75 - 1.50), and uncontrolled asthma (> 1.5) (see Additional Table 3). A woman with uncontrolled asthma had her dose increased by 1 treatment step; those with well asthma had their inhaled corticosteroid dose reduced by 1 treatment step; the intermediate group had no definite treatment change undertaken (See Additional Table 4). Women who remained uncontrolled, taking the maximum allowed dose, were assessed and their treatment decision decided by a respiratory physician
Outcomes	**Primary outcome:** total number of asthma exacerbations (moderate and severe), defined as events for which the woman sought medical attention (unscheduled visit to doctor, presentation to the emergency room or admission to hospital, or when oral corticosteroids were used). (All exacerbations occurring after randomisation were included; and those separated by 7 days or more were counted as a second event - data was collected at monthly visits, follow-up phone calls, and review of medical records) **Secondary outcomes:** exacerbation types (unscheduled visit to doctor; presentation to the emergency room; admission to hospital; oral corticosteroids use); quality of life (assessed using generic (short form 12, version 1) and disease specific (asthma quality of life questionnaire - Marks) questionnaires; asthma treatment (oral corticosteroid use; β2-agonist use; inhaled corticosteroid use; beclomethasone dipropionate equivalent inhaled corticosteroid dose; long-acting β2-agonist use; symptom-free days); lung function measures (FENO (ppb); FEV1 (L) and (%)); asthma symptoms (ACQ score (at exacerbation, at end of study); perinatal outcomes (gestational age; birthweight; birth length; birth head circumference; labour (spontaneous/induced/no labour/augmented); mode of birth (vaginal/forceps/vacuum/caesarean (elective or emergency); maternal complications (pre-eclampsia; gestational diabetes; pregnancy-induced hypertension; antepartum haemorrhage; postpartum haemorrhage; ruptured membranes; hyperemesis; proteinuria); fetal complications (stillbirth; termination of pregnancy; preterm birth; intrauterine growth restriction; jaundice; neonatal hospitalisation; congenital malformation)

	Follow-up outcomes: wheeze, bronchiolitis, croup (selected outcomes from *'A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children'.*
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "*A statistician used a computer-generated random number list*".
Allocation concealment (selection bias)	Low risk	Quote: "*Allocation to treatment algorithm group was concealed from the participant, research assistant and investigators through the use of an algorithm keeper who was not directly involved in assessment or care of women*".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "*The research assistant collected data at monthly antenatal clinic appointments, and sent this to the algorithm keeper, who applied the relevant algorithm and sent the treatment recommendation to the research assistant*". Blinding of women was assessed as successful, with most women not aware of the group to which they were assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blind to group allocation. For follow-up, the examination of the infant and interview of the primary carer was conducted by an investigator who was blinded with respect to management group and pregnancy outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/111 women withdrew from the FENO group after randomisation (3: personal reasons; 4: lost to follow-up; 1: inadequate time; 1: travel too far; 1: termination - spina bifida; 1: antenatal care elsewhere). 6/109 women withdrew from control group (3: personal reasons; 1: lost to follow-up; 1: did not like treatment adjustment; 1: asthma not seen as a problem). All women were included in final analyses, with final visit before dropping out counted as 'end of study' visit Of the 220 women in the trial, 174 (79%) consented to 12-month follow-up 146 infants attended the 12-month follow-up visit. 146/174 (82%) of the infants completed the follow-up at 12 months
Selective reporting (reporting bias)	Low risk	No obvious risk of reporting bias, with data reported for the expected outcomes (as per trial registration). For the follow-up outcomes, it is reported that 146 infants

		completed follow-up, however the table reports outcome data for only a maximum of 129 infants (67 in the FENO group and 62 in the clinical guideline group)
Other bias	Low risk	Groups well-balanced at baseline. No other obvious risk of bias identified

Silverman 2005

Methods	Randomised control trial.
Participants	219 women who were pregnant in the START Trial. The START Trial randomised 3642 women to budesonide and 3599 to placebo **Setting:** 32 countries, from October 1996 to January 1998. **Inclusion criteria:** women with symptoms at least weekly, but not as often as daily during the 3 months prior; women with reversible airway obstruction, defined as an increase in FEV1 of more than 12% after receiving a short-acting bronchodilator or as a decline in FEV1 of more than 15% on exercise testing, or as a variation of more than 15% between the 2 highest and 2 lowest PEFR recordings in a 14-day period **Exclusion criteria:** asthma symptoms; treatment for more than 2 years before entry; more than 30 days of corticosteroid treatment or more than 1 depot corticosteroid injection per year; where delaying ICS treatment was judged as inappropriate; pre-bronchodilator FEV1 < 60% of predicted; post-bronchodilator FEV1 < 80% predicted; other clinically significant disease
Interventions	**3 year 'double-blind phase' (A)** **Intervention group - inhaled budesonide (n = 102)** Once-daily 400 µg budesonide via dry powder inhaler in addition to usual asthma treatment **Control group (n = 117)** Once-daily placebo via dry powder inhaler in addition to usual asthma treatment. The placebo consisted of lactose **2 year 'open-label phase' (B)** All women received 400 µg budesonide in addition to usual therapy
Outcomes	Healthy children; adverse outcomes: spontaneous abortion, induced abortion, congenital abnormality, extrauterine pregnancy, other; preterm labour; caesarean delivery
Notes	In total 223 participants in the START Trial reported that pregnancy began during part A of the study (the 3-year double-blind phase); 4 of these women (3 taking budesonide and 1 taking placebo) were lost to follow-up. The data set thus includes 219 pregnancies (102 in the budesonide group and 117 in the placebo group)

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Silverman 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Within each stratum, patients were randomised in blocks of 10 - 5 in each treatment group, with the use of a computer program
Allocation concealment (selection bias)	Low risk	Randomisation was done at the sponsor's site by a person not involved in the analysis of data (central randomisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study inhalers were identical in appearance. Only the person responsible for the packaging knew the randomisation code
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only the person responsible for the packaging knew the randomisation code
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial included 2473 females (1250 in the budesonide group and 1223 in the placebo group) aged 15 to 50 years (there were no pregnancies in patients aged less than 15 years). In total, 223 participants reported that pregnancy began during part A of the study; 4 of these patients (3 taking budesonide and 1 taking placebo) were lost to follow-up. The data set thus includes 219 pregnancies
Selective reporting (reporting bias)	Unclear risk	Unclear from trial protocol (START trial) as to whether this analysis, and these particular outcomes were pre-specified. As per the manuscript: *"birth weight and gestational age were not recorded.*
Other bias	Unclear risk	Baseline characteristics of participants in the START study were similar between groups, however this is an analysis of a subset of individuals from the START study

Wendel 1996

Methods	Randomised controlled trial.
Participants	65 women were randomised. **Setting:** Parkland Hospital, Dallas, Texas, USA, from January 1993 to May 1994 **Inclusion criteria:** pregnant women with an acute asthma exacerbation (defined as respiratory symptoms that prompted a visit to the emergency department or prenatal clinic and that necessitated inhaled bronchodilator therapy) **Exclusion criteria:** steroid dependent asthma.
Interventions	**All women prior to randomisation:** all women received intravenous hydration with 5% dextrose in Ringer's solution. A certified respiratory therapist performed baseline pulmonary function therapy, and women received inhaled β2-agonists (maximum 3 doses of isoetharine). Women with a FEV1 of $\geq$ 70% of predicted volume on the basis of height, weight and age received outpatient management

	Women with a FEV1 < 70% of predicted volume on the basis of height, weight and age were admitted and were treated with IV hydration for at least 24 hours, and received an inhaled β2-adrenergic receptor agonist (albuterol by metered dose inhaler) every 4 hours They were then randomised to: **Inpatient intervention group - aminophylline group (n = 33)** Women received intravenous methylprednisolone 1 mg/kg every 8 hours (maximum single dose 80 mg),**along with intravenous aminophylline (5 mg/kg loading dose, then 0.5 mg/kg maintenance).** Serum theophylline concentrations were measured every 12 hours until at a therapeutic level (10-20 µg/dL). Intravenous aminophylline was continued until discharge or troublesome side effects **Inpatient control group (n = 32)** Women were given IV methylprednisolone only (as above). When FEV1 stabilised at $\geq$ 70% and there was obvious clinical improvement, intensive therapy was discontinued. Women were then discharged from hospital, and further randomised to either: **Outpatient intervention group - inhaled beclomethasone (n = 34)** Albuterol metered dose inhaler, 2 puffs every 4 hours as needed; **beclomethasone metered dose inhaler, 4 puffs twice daily;** and oral methylprednisolone taper. **Outpatient control group (n = 31)** Albuterol metered dose inhaler 2 puffs every 4 hours as needed, and oral methylprednisolone taper
Outcomes	Discontinuation of aminophylline due to adverse effects; mean hospital stay (as inpatient initially), subsequent exacerbations (failure of outpatient management with readmission for inpatient therapy); obstetric complications (including spontaneous abortion; pregnancy-induced hypertension; diabetes; asthma exacerbations in labour; caesarean delivery; induction/augmentation; chorioamnionitis; haemorrhage; meconium; postpartum infection); perinatal outcomes (Apgar score < 1 at 1 minute; at 5 minutes; cord arterial blood pH; gestational age at birth; birthweight; preterm birth; small-for-gestational age; stillbirth; neonatal death); adherence
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described in detail; quote: *"They were randomly assigned to one of two regimens as follows;"* and *"further randomized"*. Randomisation for outpatient trial was stratified according to inpatient groups
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo use and no detail of blinding - thus considered unlikely

Wendel 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No placebo use and no detail of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For the inpatient randomisation, it appears no women were lost to follow-up or excluded from analyses. Regarding the outpatient randomisation, 1/34 woman in the intervention group was lost to follow-up, and 4/31 women in the control group were lost. No other exclusions detailed
Selective reporting (reporting bias)	High risk	Perinatal and obstetric outcomes reported only overall (including some women who were not randomised and were managed as outpatients)
Other bias	Unclear risk	No detail of differences between group at baseline (inpatient randomisation or outpatient randomisation)

ACQ: asthma control questionnaire
ECG: electrocardiogram
FEF: forced expiratory flow
FENO: fraction of exhaled nitric oxide
FEV1: forced expired volume in one second
FVC: forced vital capacity
GINA: Global Initiative in Asthma
ICS: inhaled corticosteroid
IV: intravenous
PEFR: peak expiratory flow rate
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Schonberger 2004	The unit of randomisation was 'the family' and not all pregnant women included in the trial had asthma

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12613000202763

Trial name or title	The Breathing for Life Trial.
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** pregnant women at 12 to 20 weeks' gestation; physician diagnosed asthma and asthma symptoms or treatment in prior 12 months **Exclusion criteria:** inability to attend monthly study visits; inability to perform manoeuvres required for spirometry or FENO; drug or alcohol dependence; unknown dates/gestational age not confirmed by ultrasound; chronic oral steroid use or use of immunosuppressant therapy
Interventions	**Intervention group (FENO algorithm)** FENO will be measured at monthly visits during the second and third trimesters of pregnancy and the level used to adjust maintenance therapy. When FENO is high, inhaled corticosteroid therapy will be increased, when FENO is in a mid-range no change will be made, and when FENO is low, inhaled corticosteroids will be decreased. If symptoms are present, long-acting β-agonists will be added **Control group (standardised usual care)** Women will receive an initial asthma assessment, and asthma therapy will be adjusted by their usual care providers. FENO measurements will not be made
Outcomes	**Primary outcome:** adverse perinatal outcome (either preterm birth, intrauterine growth restriction, perinatal mortality or neonatal hospitalisation at birth) **Secondary outcomes:** maternal asthma exacerbations requiring medical intervention during pregnancy; maternal hospitalisations or emergency department presentations for asthma during pregnancy; maternal hospitalisations for asthma during pregnancy; preterm birth; intrauterine growth restriction; perinatal mortality; neonatal hospitalisation at birth; mean birthweight; multiple episodes of bronchiolitis in the first year of life; hospitalisation or emergency department presentation for severe respiratory illness (bronchiolitis, croup or wheezing) in the first year of life; multiple episodes of croup in the first year of life; hospitalisation for bronchiolitis in first year of life; atopy at age 3; physician diagnosed asthma at age 6
Starting date	5/03/2013.
Contact information	Professor Peter Gibson: Centre for Asthma and Respiratory Diseases Level 2, West Wing Hunter Medical Research Institute, Locked Bag 1, HRMC Newcastle, New South Wales 2310, Australia +61 02 40420143 peter.gibson@hnehealth.nsw.gov.au
Notes	Target sample size: 1180.

ACTRN12613000244707

Trial name or title	Antenatal Asthma Management Service (AAMS).
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** women at less than 20 weeks' gestation, who have asthma which has been previously diagnosed by a doctor and is not currently in remission; aged 18 to 45 years; expected to give birth to a

ACTRN12613000244707 (*Continued*)

	singleton and able to speak English **Exclusion criteria:** previous participation in an asthma study run at the hospital or a pre-existing chronic medical condition (i.e. diabetes, hypertension, cardiac disease, HIV/hepatitis, renal disease, haematology disorder (i.e. thalassaemia, thrombophilia), thyroid disorder, psychiatric disease requiring therapy with antidepressant or antipsychotic, epilepsy)
Interventions	**Intervention group** Women will receive care through the nurse-led Antenatal Asthma Management Service, based in the antenatal outpatient clinic. The Antenatal Asthma Management Service will be led by a respiratory nurse with qualifications in asthma management and education and spirometry. All women will receive asthma education with a full assessment of their asthma at 18, 24, 30 and 36 weeks' gestation conducted by a respiratory nurse. Each antenatal visit will include a 60-minute session where asthma management skills will be assessed. In addition, women will receive education about asthma control and management skills including trigger avoidance and smoking cessation counselling when appropriate. During the first visit at 18 weeks, all women will be provided with a written asthma action plan. Current asthma management therapies will be evaluated and recommendations regarding optimal therapy made if required. A detailed asthma management report will be forwarded to the woman's preferred family physician who will review and assess appropriateness of recommended changes in therapy. This preferred provided will be the lead clinician responsible for the woman's asthma in pregnancy **Control group** Standard care will be as outlined in the South Australian Perinatal Practice Guidelines, which involves women self-managing their disease and seeking guidance for management when required from a midwife, obstetrician, respiratory physician or GP
Outcomes	**Primary outcome:** asthma exacerbations (moderate and severe) defined as events for which the woman sought medical attention (i.e. an unscheduled visit to a doctor, presentation to the emergency department room or admission to hospital, or when oral corticosteroids were used for treatment of asthma) **Secondary outcomes: for the mother:** ACQ score and FEV1 throughout gestation for the mother; asthma-related quality of life; perceived control of asthma; medication adherence; asthma knowledge; hypertensive disorders of pregnancy; antepartum haemorrhage; gestational diabetes; preterm labour; need for antenatal hospitalisation; weight gain during pregnancy; chorioamnionitis requiring antibiotics during labour; length of postnatal stay; use of postnatal antibiotics; postpartum haemorrhage (of greater than 500 mL); emergency caesarean; **for the infant/child:** gestational age at birth; preterm birth; birthweight; birth length; head circumference; intrauterine growth restriction; birthweight percentile; Agpar scores, congenital malformations; admission to neonatal intensive care unit or special care nursery; stillbirth
Starting date	Trial registered 28/02/2013.
Contact information	Associate Professor Vicki Clifton: The Robinson Institute, The University of Adelaide, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale, South Australia 5112, Australia +61 8 8133 2133 vicki.clifton@adelaide.edu.au
Notes	Target sample size: 378.

ACTRN12613000301763

Trial name or title	Dietary modification for asthma control in pregnancy.
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** pregnant women with mild or moderate/severe asthma currently using inhaled corticosteroids; older than 18 years; poor diet quality (less than 1 serving/day fruit and less than 2 servings/day vegetable, determined from Food Frequency Questionnaire) **Exclusion criteria:** recent (past month) respiratory tract infection; intermittent asthma; current smoker; use of antioxidant supplements; previous pregnancy complications including growth restriction, stillbirth or preterm delivery
Interventions	At approximately 14 weeks' gestation, the 4-week run-in period (prior to the 12 week intervention) will commence in which all women will be provided with individual asthma management, education and advice (by a respiratory nurse), and will complete a food frequency questionnaire. At 18 weeks, women will be randomised to the intervention or control **Intervention group** Women will receive a copy of the same booklet received in standard care (see below). Women will be counselled on types of antioxidant-rich foods to purchase and consume, including fruits, vegetables, and lean meat; women will also be provided with a list of foods high in antioxidants, and asked to identify which of the foods they are most likely to purchase and consume over the 12 weeks. Women will be given meal/snack suggestions to assist compliance. A shopping voucher of $30 per week per woman will also be provided to contribute to the cost of fruits, vegetables, whole grains and lean meats **Control group** The control group will receive standard care which includes a booklet on "Healthy Eating During Pregnancy", which contains the recommended number of servings of each food group to be consumed during pregnancy (according to the 2013 Australian Dietary Guidelines), as well as further information on key nutrients during pregnancy, supplements, weight gain and guidance on, for example, alcohol, caffeine and water. No other dietary education will be provided to this group
Outcomes	**Primary outcome:** asthma control score, using the validated ACQ. **Secondary outcomes:** plasma circulating concentrations of antioxidants; markers of oxidative stress (plasma 8-F2 isoprostanes); exhaled FENO; time to, and number of, exacerbations: asthma exacerbations during pregnancy (moderate and severe exacerbations) defined as events for which the participant sought medical attention (i.e. an unscheduled visit to a doctor, presentation to the emergency department room or admission to hospital, or when oral corticosteroids were used for treatment of asthma)
Starting date	Trial registered: 19/03/2013.
Contact information	Associate Professor Vicki Clifton: The Robinson Institute, The University of Adelaide, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale, South Australia 5112, Australia +61 8 8133 2133 vicki.clifton@adelaide.edu.au
Notes	Target sample size: 104.

ACTRN12613000800729

Trial name or title	Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy (MASTERY)
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** pregnant women aged 18 years and older who can communicate in English. Women will be included if they have asthma and used any asthma medications in 12 months before pregnancy and/or during their current pregnancy **Exclusion criteria:** women with asthma who are unable to communicate in English or cannot use a smart mobile phone (iPhone or Android)
Interventions	**Intervention group** Women will be provided with a COPD-6 and a specifically designed Breathe-easy application installed on their mobile phone. They will be asked to measure their lung function using the COPD-6 device twice daily and to record their asthma symptoms and medication usage in Breathe-easy. The lung function data will be transmitted to a central server and reviewed by the researcher daily. The data will also be sent to participants' general practitioners. Women and the research team will have secure access to the online portal. Any clinically significant reduction in lung function will be brought to the attention of the participants' general practitioners in order for them to determine if any medication changes or unscheduled visit related to asthma are needed. The total duration of the intervention will be 7 to 9 months depending on when the participants had their first antenatal visit **Control group** The control group will receive usual medical care provided by the antenatal clinics and/or their health professionals
Outcomes	**Primary outcome:** asthma control as measured by Juniper's ACQ. **Secondary outcomes:** quality of life on Juniper's Mini Asthma Quality of Life Scale; asthma-related health visits; preventer to reliever use ratio; asthma-related days off work/study; gestational age at birth; development of antenatal complications, such as hypertensive disorders of pregnancy, antepartum haemorrhage and gestational diabetes; birthweight; Apgar scores
Starting date	12/08/2013.
Contact information	Dr Johnson George: Centre for Medicine Use and Safety Faculty of Pharmacy and Pharmaceutical Sciencesm Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia +61 3 9903 9178 Johnson.George@monash.edu
Notes	Target sample size: 70.

NCT01345396

Trial name or title	Influence of an Asthma Education Programme on Asthma Control During Pregnancy
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** pregnant woman; less than 20 weeks of gestation; diagnosis of asthma before the pregnancy (clinical history and specific medications used); agreement to enter into the study **Exclusion criteria:** pregnant woman (more than 20 weeks of gestation at the inclusion time); history of major respiratory problems during previous pregnancy; refusal to enter into the study

NCT01345396 (*Continued*)

Interventions	**Intervention group (health education about asthma)** Women will receive 3 face-to-face appointments (at less than 20, 36 weeks' gestation, and 12 weeks after birth). Topics: What is asthma? What influence the course of asthma? How to monitor it? How to manage it? **Control group** Women will receive no education.
Outcomes	**Primary outcome:** level of asthma control (ACQ). **Secondary outcomes:** number of unscheduled visits to the doctor for asthma; quality of life; knowledge about asthma
Starting date	02/2010.
Contact information	Professor Vincent Ninane: Centre Hospitalier Universitaire Saint Pierre, Brussels, Belgium
Notes	Target sample size: 80.

ACQ: Asthma Control Questionnaire
FENO: fraction of exhaled nitric oxide
FEV1: forced expired volume in one second

DATA AND ANALYSES

Comparison 1. Inhaled magnesium sulphate versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma exacerbations ("frequency of acute asthma exacerbation till delivery")	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Lung function (FEV1 (%))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Lung function (FVC (%))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Lung function (FEV1/FVC (%))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Lung function (FEF25%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Lung function (FEF75%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 PEF (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Caesarean birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Intravenous theophylline versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation of intervention due to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Stillbirth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Neonatal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Preterm birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Length of hospitalisation for the mother (days)			Other data	No numeric data

Comparison 3. Inhaled corticosteroid versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma exacerbations	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.13, 1.05]
1.1 Beclomethasone (four puffs, twice daily)	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.13, 1.05]
2 Caesarean birth	2	314	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.57, 4.79]
2.1 Beclomethasone (1 mg daily)	1	95	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.62]
2.2 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Random, 95% CI)	3.15 [1.04, 9.60]
3 Adherence with intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

3.1 Beclomethasone (four puffs, twice daily)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.94, 1.07]
4 Induced abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.24]
5 Spontaneous abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.75, 3.25]
6 Stillbirth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Beclomethasone (four puffs, twice daily)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Neonatal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Beclomethasone (four puffs, twice daily)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Preterm birth	2	314	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.43, 1.63]
8.1 Beclomethasone (1 mg daily)	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.16]
8.2 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.24, 2.12]
9 Birthweight (g)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Beclomethasone (1 mg daily)	1	95	Mean Difference (IV, Fixed, 95% CI)	-34.0 [-290.17, 222.17]
10 Apgar score less than seven	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Beclomethasone (1 mg/day)	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.06, 14.57]
11 Congenital malformation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Budesonide (400 µg/day)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.03, 2.52]
12 "Obstetric complications"	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Beclomethasone (1 mg daily)	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.59]
13 "Perinatal complications"	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Beclomethasone (1 mg daily)	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.71, 2.81]
14 "Healthy children delivered"	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.15]
15 "Other adverse outcomes"	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Budesonide (400 µg daily)	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.13, 4.49]

Comparison 4. Inhaled corticosteroid versus oral theophylline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma exacerbations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Asthmatic symptoms at delivery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Asthmatic symptoms (nocturnal)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Asthma medication requirements (rescue oral corticosteroids for exacerbation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

5 Asthma medication requirements (albuterol puffs per day)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Lung function (proportion of study visits with FEV1 < 80% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Lung function (proportion of study visits with PEFR < 80% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Pre-eclampsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Caesarean birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Postpartum haemorrhage (blood loss > 500 mL for vaginal birth and > 1 L for caesarean)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Chorioamnionitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Adverse effects attributed to intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Nausea	1	385	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.11, 1.00]
12.2 Nervousness	1	385	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.61]
12.3 Insomnia	1	385	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.61]
12.4 Tremor	1	385	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.18]
12.5 Palpitations	1	385	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.88]
12.6 Heartburn	1	385	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 72.06]
13 Discontinuation of intervention due to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14 Adherence with intervention (self-reported compliance)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15 Adherence with intervention (measured compliance)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16 Perinatal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17 Gestational age at birth (weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18 Preterm birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19 Birthweight (g)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20 Low birthweight (< 2500 g)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21 Small-for-gestational age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22 Neonatal sepsis (discharge diagnosis of sepsis)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23 Congenital malformation (major)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24 Antenatal admissions to hospital for the mother (associated with exacerbation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25 Emergency department visits for the mother (associated with exacerbation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 5. FENO algorithm versus clinical guideline algorithm to adjust asthma therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma exacerbations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Admission to neonatal intensive care unit or special care nursery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Asthmatic symptoms (ACQ score)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Asthmatic symptoms (symptom-free days)			Other data	No numeric data
5 Asthma medication requirements (inhaled corticosteroids)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Asthma medication requirements (long-acting β2-agonists)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Asthma medication requirements			Other data	No numeric data
8 Lung function			Other data	No numeric data
9 Quality of life			Other data	No numeric data
10 Pregnancy-induced hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Pre-eclampsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Gestational diabetes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13 Caesarean birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Elective	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.63]
13.2 Non-elective	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.36, 1.55]
14 Antepartum haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15 Postpartum haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16 Ruptured membranes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17 Hyperemesis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18 Termination of pregnancy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19 Stillbirth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20 Gestational age at birth (weeks)			Other data	No numeric data
21 Preterm birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22 Birthweight (g)			Other data	No numeric data
23 Low birthweight (< 2500 g)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24 Small-for-gestational age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25 Jaundice	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26 Congenital malformation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27 Bronchiolitis (multiple versus one or no episodes)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28 Croup (multiple versus one or no episodes)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 6. Pharmacist-led multi-disciplinary approach to management of maternal asthma (MAMMA) versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma exacerbations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Admission to neonatal intensive care unit or special care nursery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Asthmatic symptoms (ACQ score)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 3 months	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.54, 0.20]
3.2 6 months	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.83, -0.29]
3.3 3 months - baseline	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.76, 0.14]
3.4 6 months - baseline	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.15, -0.27]
4 Asthmatic symptoms (ACQ score)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 ACQ score < 1.5 (adequately controlled asthma)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.12, 1.84]
5 Asthma medication requirements (oral corticosteroids)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Asthma-related days off work	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Hypertension during pregnancy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Gestational diabetes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Caesarean birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Gestational age at birth (weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11 Preterm birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Birthweight (g)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13 Small-for-gestational age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14 Apgar score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 1 minute	1	58	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.04, 1.44]
14.2 5 minute	1	58	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.07, 0.67]
15 Congenital malformation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16 Asthma-related hospital admissions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17 Asthma-related emergency visits	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 7. Progressive muscle relaxation (PMR) versus sham training

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung function (FEV1 (L))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Lung function (PEFR (L/minute))	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Quality of life (STAXI scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 State-Anger	1	64	Mean Difference (IV, Fixed, 95% CI)	-3.90 [-5.64, -2.16]

3.2 Trait-Anger	1	64	Mean Difference (IV, Fixed, 95% CI)	-5.60 [-7.42, -3.78]
3.3 Anger-In	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.82, 0.62]
3.4 Anger-Out	1	64	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-4.55, 0.55]
3.5 Anger-Control	1	64	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.75, 2.75]
4 Quality of life (SF-36 health survey scores)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Physical functioning	1	64	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.23, 4.23]
4.2 Role physical	1	64	Mean Difference (IV, Fixed, 95% CI)	7.0 [3.88, 10.12]
4.3 Bodily pain	1	64	Mean Difference (IV, Fixed, 95% CI)	3.10 [-1.46, 7.66]
4.4 General health perceptions	1	64	Mean Difference (IV, Fixed, 95% CI)	4.30 [-0.24, 8.84]
4.5 Vitality	1	64	Mean Difference (IV, Fixed, 95% CI)	7.70 [3.67, 11.73]
4.6 Social functioning	1	64	Mean Difference (IV, Fixed, 95% CI)	12.80 [8.50, 17.10]
4.7 Role emotional	1	64	Mean Difference (IV, Fixed, 95% CI)	12.20 [8.09, 16.31]
4.8 Mental health	1	64	Mean Difference (IV, Fixed, 95% CI)	6.10 [1.84, 10.36]

ADDITIONAL TABLES

Table 1. Dose changes based on FENO and ACQ results for the FENO intervention algorithm (Powell 2011)

	FENO concentration (ppb)	Symptoms (ACQ score)	ICS dose change	β2-agonist dose change
Level 1	> 29	NA	ICS x 1 step	No change
Level 2	16 - 29	≤ 1.5	No change	No change
Level 3	16 - 29	> 1.5	No change	LABA x 1 step
Level 4	< 16	≤ 1.5	ICS x 1 step	No change
Level 5	< 16	> 1.5	ICS x 1 step	LABA x 1 step

ACQ: asthma control questionnaire
FENO: fraction of exhaled nitric oxide
ICS: inhaled corticosteroid
LABA: long-acting β2 agonist
NA: not part of the assessment at this FENO level

Table 2. FENO algorithm treatment steps (Powell 2011)

	ICS step	β2 step
Step 1	0	Salbutamol as required
Step 2	Budesonide 100 µg twice per day	Formoterol 6 μg twice per day
Step 3	Budesonide 200 µg twice per day	Formoterol 12 μg twice per day
Step 4	Budesonide 400 µg twice per day	Formoterol 2 × 12 μg twice per day

Table 2. FENO algorithm treatment steps (Powell 2011) (*Continued*)

Step 5	Budesonide 800 µg twice per day	Formoterol 2 × 12 μg twice per day

FENO: fraction of exhaled nitric oxide
ICS: inhaled corticosteroid

Table 3. Dose changes based on clinical assessment for the clinical algorithm (control) (Powell 2011)

	ACQ score	Treatment adjustment
Level 1	> 1.5	1 step
Level 2	0.75 - 1.5	No change
Level 3	< 0.75	1 step

ACQ: asthma control questionnaire

Table 4. Clinical algorithm treatment steps (Powell 2011)

	Treatment
Step 1	Salbutamol as required
Step 2	Budesonide 200 μg twice per day
Step 3	Budesonide 400 μg twice per day
Step 4	Budesonide 400 μg and formoterol 12 μg twice per day
Step 5	Budesonide 800 μg and formoterol 24 μg twice per day

CONTRIBUTIONS OF AUTHORS

Emily Bain and Kristen Pierides developed the protocol. Philippa Middleton, Caroline Crowther, Vicki Clifton, Michael Stark and Nicolette Hodyl made comments and contributed to the subsequent drafts of the protocol.

Emily Bain and Kristen Pierides assessed the citations and studies found for inclusion, assessed risk of bias and conducted data analyses. Philippa Middleton, Caroline Crowther, Michael Stark, Nicolette Hodyl and Vicki Clifton assisted with data interpretation and edited and commented on the review.

DECLARATIONS OF INTEREST

Vicki Clifton was an investigator on the 'Managing Asthma in Pregnancy (MAP)' Study (Powell 2011). All tasks relating to this study (assessment of eligibility for inclusion, assessment of risk of bias, data extraction) were carried out by other members of the review team who were not directly involved in the trial. Vicki Clifton is also an investigator on two of the ongoing trials (ACTRN12613000244707; ACTRN12613000301763), and Philippa Middleton is an investigator on one of these trial (ACTRN12613000244707). Therefore, in future updates of this review, all tasks relating to these studies (assessment of eligibility for inclusion; and if included, assessment of risk of bias, data extraction etc.) will be carried out by other members of the review team who are not directly involved in the trials.

None known for other authors.

SOURCES OF SUPPORT

Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added a number of additional secondary outcomes for the fetus/neonate (respiratory distress syndrome, intraventricular haemorrhage, periventricular haemorrhage, chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, patent ductus arteriosus, hypothalamo-pituitary-adrenal (HPA) axis function (however defined by authors) and hyperbilirubinaemia), as they were considered important, relating to possible consequences of maternal asthma and/or the pharmacological management of maternal asthma.

In recognition of the importance of long-term follow-up of the infant into childhood and adulthood, we have also added a number of secondary review outcomes for the infant as a child and adult (death, any neurodevelopmental disability, growth assessments, lung function, respiratory morbidity, blood pressure, glucose intolerance/insulin sensitivity, dyslipidaemia, HPA axis function, age at puberty, bone density, visual impairment, hearing impairment, developmental delay, intellectual impairment, cerebral palsy, motor delay or impairment, educational achievement, behavioural/learning difficulties), relating to possible health consequences associated with maternal asthma, including the pharmacological management of asthma during pregnancy.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [administration & dosage]; Algorithms; Anti-Asthmatic Agents [therapeutic use]; Asthma [*therapy]; Beclomethasone [therapeutic use]; Magnesium Sulfate [administration & dosage]; Muscle Relaxation; Nitric Oxide [administration & dosage]; Pregnancy Complications [*therapy]; Randomized Controlled Trials as Topic; Theophylline [therapeutic use]

MeSH check words

Female; Humans; Pregnancy