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Title: Strategies towards improving pharmacological management of asthma during pregnancy

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Abstract

Maternal asthma represents a significant burden to individuals and the healthcare system, affecting 1 in 10 pregnancies worldwide. Approximately 50% of asthmatic women experience a deterioration of asthma control at some stage during pregnancy, with a number requiring use of oral corticosteroids for the management of acute exacerbations. The presence of maternal asthma and exacerbations during pregnancy is a noted risk factor for a range of adverse perinatal outcomes including preterm birth, small-for-gestational age, pre-eclampsia, and gestational diabetes. These negative impacts highlight the need for evidence-based approaches for improving asthma management during pregnancy and subsequent perinatal outcomes. Despite this, relatively small progress has been made in enhancing the management of maternal asthma in the clinical setting. A major challenge in improving outcomes of asthmatic pregnancies is that there is no single simplified approach for improving outcomes, but rather the requirement to consider the dynamic relationship between a myriad of interrelated factors that ultimately determine an individual's ability to maintain adequate asthma control. Understanding how these factors are impacted by pregnancy and how they can be addressed through various interventions is therefore important in optimizing health outcomes. This review summarises key factors involved in influencing outcomes associated with maternal asthma. This includes an overview of the use of asthma medications in pregnancy, while also considering the impacts of interrelated aspects such as medication adherence, health-seeking behaviours, biological and lifestyle factors, co-morbidities, and asthma self-management strategies on asthma control. Addressing such factors through multidisciplinary approaches towards treatment have potential to improve the health of mothers and their offspring. Optimising asthma control should be a high priority within the antenatal setting, with women advised about the importance of good asthma control,

managing asthma actively throughout pregnancy by utilising their asthma medications, and managing exacerbations in a timely and effective manner.

Key Words: Pregnancy; asthma; inhaled corticosteroids; medications

1. Introduction

Maternal asthma represents a significant burden to individuals and the healthcare system. Asthma is one of the most common chronic medical conditions in pregnancy, complicating an estimated 8-13% of pregnancies worldwide.[1] There is clear evidence that maternal asthma is associated with significant perinatal morbidity and mortality, with 20-50% increased risk of adverse perinatal outcomes including low birth weight, small-for-gestational age, preterm birth, pre-eclampsia, and gestational diabetes.[2, 3] Given the increased risk of adverse pregnancy outcomes, it is perhaps not unsurprising that maternal asthma has also been associated with long-term adverse effects on the health of the offspring, including an increased risk of a wide spectrum of non-communicable diseases in the offspring.[4]

These negative impacts highlight the need for evidence-based approaches for improving asthma management during pregnancy and subsequent perinatal outcomes. Despite this, only relatively small progress has been made in enhancing the management of maternal asthma in the clinical setting. A major challenge in improving outcomes of asthmatic pregnancies is that there is no single simplified approach for improving outcomes, but rather the requirement to consider the dynamic relationship between a myriad of interrelated factors that ultimately determine an individual's ability to maintain adequate asthma control.

Understanding how these factors are impacted on by pregnancy and how they can be addressed through various interventions is therefore important in optimizing health outcomes. For this reason, in this review we have chosen to provide an overview of what we believe to be some of key factors involved in influencing outcomes associated with maternal asthma. This involves looking beyond asthma medications and considering interrelated aspects such as health-seeking behaviours, asthma self-management, medication adherence, biological and lifestyle factors and co-morbidities. A description of the etiology, pathogenesis, and typical

management of asthma in general adults is beyond the scope of this review and can be found elsewhere.[5]

2. Overview of asthma treatment in pregnancy

The determination of safety of asthma medications in pregnancy is largely limited to observational studies, limiting the ability to precisely distinguish the impacts of asthma treatments from those of maternal asthma. Despite this challenge, there is a growing body of literature supporting the safety of various asthma medications during pregnancy, with a prevailing belief that uncontrolled asthma during pregnancy poses greater short and long-term risk to the mother and her baby. A summary of asthma medications with respect to their usual doses, adverse events, and safety during pregnancy is presented in Table 1. The greatest amount of evidence exists for the use of inhaled corticosteroids in pregnancy, but there is increasing evidence to support the use of ICS combined with LABA.[6] Therefore there is no reason that women who enter pregnancy on a combined ICS + LABA should necessarily be switched to an ICS alone preparation. Existing recommendations are that asthma be managed during pregnancy in the same manner as a non-pregnant adult, including management of asthma medications.[7] This means selecting medication and delivery devices that meet patient's needs and circumstances, with therapy divided into the use of long-term control medications to prevent asthma manifestations and the use of rescue therapy to provide immediate relief of symptoms. In accordance with non-pregnant adults, asthma control should be regularly assessed and preventer medications adjusted accordingly at regular intervals to maintain adequate symptom control. An approach towards the adjustment of asthma therapies in pregnancy is outlined in Figure 2. Given the high prevalence of poor medication adherence in pregnancy, it is critical that this aspect is evaluated prior to any recommendations to step up treatment. Further, among non-pregnant adults there is a general recommendation to consider stepping down therapy in situations where asthma is stable and

has been well controlled for 2-3 months, but evidence to support this strategy in pregnancy is very limited. Therefore consideration to stepping down treatment should only be considered if the woman is taking an inappropriately high dose of a medicine and should be done under careful supervision.

3. Course of asthma in pregnancy

Pregnancy is recognized as a major challenge in the management of asthma as it can alter the course of asthma severity and its treatment, which in turn has the potential to influence pregnancy outcomes. Recent data demonstrates that half of all women experience a loss of asthma control during pregnancy, with approximately 1 in 5 experiencing a moderate to severe exacerbation.[8] Explanations for this clinical observation are unclear, but could relate to a range of interconnecting factors, as outlined in **Figure 1**. Outside of pregnancy, it is well recognised that a number of factors impact on asthma control. Each of these factors in turn can be influenced by pregnancy, providing some explanation for changes in asthma control. For example, pregnancy is a time of significant change, including physiological, behavioural, and biological, with women interacting with the healthcare system with significantly greater frequency than they likely did prior to pregnancy. The impact of each of these factors on asthma management is outlined below.

3.1.Medication adherence

While the continuation of usual asthma medications during pregnancy is recommended in clinical guidelines, it is not uncommon for women to cease their asthma medications, with or without consultation with healthcare professionals.[9] This is of significant concern given that

non-adherence to medication has been identified as a key factor involved in worsening asthma during pregnancy.[10] Decisions regarding the cessation of asthma medications during pregnancy may be driven through a perceived lack of benefit in continuing medications, insufficient support and education from healthcare professionals regarding the use of asthma medications during pregnancy, or concerns regarding the safety of asthma medications during pregnancy.[11] In the prospective cohort study by Murphy et al. 40% of women reported non-adherence to inhaled corticosteroids. [12] Reduced medication adherence to short-acting beta-agonists may also be a concern in pregnancy, but data relating to the potential extent of this problem are not available.

3.2 Healthcare provider interaction

Generally speaking, pregnancy presents an opportunity for women to interact with the healthcare system at a greater frequency than they would have previously. Increased interaction with healthcare providers means increased opportunity to evaluate and advise on asthma control. However, this relies on the healthcare provider's awareness of the importance of optimal asthma management during pregnancy and their training on how to educate and support pregnant women. A recent Australian survey of general practitioners highlight a significant lack of confidence or knowledge regarding the management of asthma during pregnancy.[13] Among survey respondents, a quarter (25.8%) indicated that they would advise pregnant women to decrease or discontinue asthma medications. Inadequate management practices also extend to the hospital setting, with a previous prospective cohort study demonstrating that despite presenting to the emergency department with similar asthma severity, compared to non-pregnant women, pregnant women were less likely to be treated with oral corticosteroids and experienced a 2.9 (95%CI 1.2-6.8) times greater likelihood of

reporting an ongoing exacerbation two weeks later.[14] Such findings are not unique to medical practitioners, with a recent study involving midwives identifying feelings of uncertainty and a lack of confidence in antenatal asthma management.[15] Notably, midwives who reported having greater knowledge in asthma management also reported playing a greater role in antenatal asthma management. These studies highlight the importance of education programs targeting healthcare professionals involved in the provision of antenatal care and having integrated systems in place to ensure pregnant women with asthma receive the additional support and care they require.

3.3 Physiological and Biological changes

Pregnancy is a time of significant physiological change, with marked changes in kidney, liver, cardiovascular, respiratory and immunological function orchestrated by alterations in the endocrine system and the release of various hormones and growth factors into the maternal circulation by the placenta.[16] Such adaptations aim to provide an optimal environment for the fetus to grow and develop, yet data suggests asthma may worsen in pregnancy due to these physiological adaptations. Immunological adaptations are the most studied and likely factors contributing towards worsening asthma control in pregnancy. Pregnancy induced changes in immune function may promote worsening of asthma control via the activation of chemokine pathways and increased circulating levels of monocytes and neutrophils (Osei-Kumah et al 2005, 2008. 2009).[17, 18] Furthermore there is increasing evidence of several sex-specific strategies by which the fetus copes with presence of maternal asthma *in utero*.[19] These adaptations have recognised importance for the management of maternal asthma during pregnancy.

Fetal sex has been implicated as a risk factor for worsening asthma in pregnancy, with pregnant women carrying a female fetus having poorer asthma control compared to women carrying a male fetus.[20] While the exact mechanism linking fetal sex with maternal asthma control remains uncertain, it is hypothesised that it may occur through sex specific differences in placental function that differentially influence maternal physiology and the course of maternal asthma in pregnancy. The sex specific differences in placental function in pregnancies complicated by asthma may also influence neonatal outcomes. Some of these differences could be due to noted sex-specific differences in placental growth, development and function, including nutrient transport, energy metabolism, and endocrine function.[21] A large body of data has demonstrated that male and female placentae adapt differently to the presence of maternal asthma by adjusting placental sensitivity to endogenous glucocorticoids and affecting placental glucocorticoid regulated pathways that are central to fetal growth and development.[22] In short, males induce a state of glucocorticoid resistance in response to maternal asthma in order to continue to grow in an adverse environment. This adaptation poses a significant risk in presence of an acute asthma exacerbation with males more likely to deliver preterm, be growth restricted or stillborn. Females remain sensitive to the effects of glucocorticoids which result in reduced growth but a greater chance of surviving to term if mothers exacerbate.[22] Most importantly, the control of maternal asthma with ICS is protective against these sex specific effects and both and male and female fetuses grow normally when asthma is controlled and outcomes are comparable to a non-asthmatic population.[23] These data suggest fetal sex may pose a challenge not only in influencing the course of asthma during pregnancy, but also in influencing its impact on subsequent pregnancy outcomes. Given evidence that the course of pregnancy and its associated adverse impacts may be influenced by fetal sex, this highlights that subsequent investigation of

interventions aimed at improving perinatal outcomes should consider fetal sex in their evaluation.

The previously outlined physiological changes that occur during pregnancy can also introduce challenges in the assessment of asthma, with pregnancy-related factors such as dyspnoea of pregnancy, which can occur in up to 70% of pregnancy women, potentially confused with asthma-related symptoms.[6] Theoretically, hormonal, metabolic, and physiological changes during pregnancy could alter the mechanics of breathing and pulmonary function in pregnant women which may change across the duration of pregnancy, but evidence relating to the magnitude and significance of such changes is unclear and often inconsistent.[24] Therefore, at this stage the general recommendations are that lung function can be assessed and monitored as for non-pregnant adults, with the exception of methacholine challenge testing which is not recommended during pregnancy.[6] Beyond direct evaluation of pulmonary function, there are a range of tools available for evaluating asthma control in adults, but concerns regarding their applicability and validity for use in pregnancy have been raised due to challenges related to attributing symptoms to pregnancy or underlying asthma.[25] Most recently, however, a modified version of the Asthma Control Test, where additional focus is placed on identifying shortness of breath due to asthma rather than dyspnoea of pregnancy, has been demonstrated as being reliable and valid for evaluating asthma control in pregnancy.[25]

3.4 Lifestyle changes

Pregnancy is a time when women commonly enact a range of positive behavioural changes, frequently out of desire to improve outcomes of their unborn child and often with the support and encouragement of antenatal care providers. Examples of such include reduction or cessation of cigarette use or changes in diet and exercise.

Smoking cessation in particularly has been a major focus of educational programs offered within antenatal care settings. Given the associated harmful impacts of smoking on asthma control, interventions focused on smoking cessation among asthmatic women are likely to be even more effective in improving health outcomes.[26] How these benefits are obtained, however, requires greater attention. According to data from a prospective cohort study of asthmatic women, 29% of smokers ceased smoking during early pregnancy through usual antenatal care support mechanisms.[27] In contrast, among those who received additional support through a nurse-led antenatal asthma management program, 54% stopped smoking in early pregnancy. Therefore, the impact of various smoking cessation strategies may vary dramatically in terms of how they operate and target individuals, but should remain a key focus for improving perinatal outcomes in asthmatic pregnancies.

Maternal diet represents another area where changes commonly occur during pregnancy.[28] These changes include alterations in consumption (both increases and decreases) of certain foods (e.g. reduction in foods at risk of listeria or mercury contamination, increase in healthy foods such as fruit) as well as general increases in dietary supplement intake (e.g. folate, vitamin D, omega 3 fatty acids, iodine, multivitamins).[29] Such changes in dietary intakes could have important implications for alterations in asthma control during pregnancy. Some of these changes have been hypothesised to occur through alterations in oxidative stress.[30] Dietary intervention studies among non-pregnant adults have demonstrated protective impacts of antioxidants in asthma, but no such studies have been undertaken in pregnancy.[30] Observational data are available, however, to support such an intervention, with evidence that pregnant women with moderate to severe asthma have altered circulating concentrations of antioxidants compared to women with mild or no asthma, whereas low antioxidant concentrations were associated with reduced fetal growth among asthmatic pregnancies.[31] In addition, while the impact of dietary patterns has not been extensively

explored in pregnancy, pre-conception intake of a high fat/sugar/takeaway diet has been associated with an increased likelihood of uncontrolled asthma during pregnancy.[32]

Lastly, interventions aimed at improving exercise in pregnancy have demonstrated positive effects in reducing the risk of excessive gestation weight gain and risk of adverse pregnancy complications.[33] While data on the impacts of such exercise interventions on asthma control in pregnancy are absent, a recent randomized controlled trial in non-pregnant obese adults demonstrated that the addition of exercise to a short-term weight-loss program led to significant improvements in asthma control and anti-inflammatory biomarkers, as well as reductions in airway and systemic inflammation.[34] Therefore, further research to identify whether dietary and exercise interventions can improve asthma control in pregnancy are warranted.

3.5. Co-morbidities

Comorbidities are common and are being increasingly recognized as playing an important role in influencing outcomes in individuals with asthma. Such common comorbidities include gastro-esophageal reflux disease, mental illness, obesity, and allergic rhinitis. While some of these factors may not appear immediately modifiable, especially within an obstetric setting, awareness of the contribution of these factors to impaired asthma control is important. Just as concerns regarding medication safety can impact on adherence to asthma medications during pregnancy, they could also have the same effect on medications used in the management of other co-morbidities. Clinicians should be aware of the increased likelihood of these co-morbidities among women with asthma and the requirement for comprehensive assessment, treatment, or referral as appropriate.

Rhinitis is perhaps one of the most common co-morbidities. In a recent prospective clinical trial, rhinitis occurred in 65% of pregnant asthmatic women , with 20% of women experiencing rhinitis only during pregnancy.[35] While rhinitis symptoms improved as pregnancy progressed, the presence of rhinitis was associated with poorer asthma control and anxiety. Further, atopic rhinitis was associated with poorer lung function. A separate study in the same cohort of women identified a higher prevalence of asthma exacerbations among women who were overweight (51%) or obese (48%) compared with healthy weight women (25%; P=0.026).[36] Pregnancy related weight gain appeared to have no impact on exacerbation risk.[36] Further investigations revealed that maternal overweight or obesity was associated with altered macrophage activation and that altered macrophage activation was associated with an increased risk of exacerbations requiring oral corticosteroids.[36]

A prospective cohort study undertaken within a socially disadvantaged population in Australia identified that women with a self-reported history of depression or anxiety were much more likely to experience poor asthma control during pregnancy.[37] These findings are supported by those of two previous studies which identified that anxiety was an independent risk factor for poor asthma control and exacerbations.[38, 39] Further, women's perception of asthma control in early pregnancy reduced the risk of subsequent exacerbations.[39] It is unclear whether these associations are reflective of behavioural, social, or biological factors or the combination of all three associated with the presence of a mental health illness. What evidence it does provide, however, is the identification of a group of higher risk women who are already recognised at being at increased risk of adverse perinatal outcomes and so could benefit from additional attention and support. Strategies aimed at addressing such key psychosocial factors, such as reducing treatment-related anxiety, may help improve asthma control and related pregnancy outcomes.

4. Interventions for improving asthma management in pregnancy

An improved understanding of the unique interplay between pregnancy and asthma has led to the investigation of strategies aimed at improving asthma related outcomes. While a number of different interventions have been trialed, including self-management education, and individualized asthma management plans according to airway inflammation status, there is a lack of data associating these interventions with improvements in perinatal outcomes.[40]

4.1 Asthma Education and Self-Management Skills

Self-management programs are designed to facilitate the acquisition of preventive or therapeutic health care activities by patients through the provision of education by healthcare professionals which in turn assists in the adoption of health-promoting behaviours.[41] A number of studies have investigated the impact of providing asthma self-management education in pregnancy on asthma related outcomes.[12, 27, 42, 43] These services incorporate education, self-monitoring, regular review with optimisation of pharmacotherapy, and written asthma action plans for management of unstable asthma. In one prospective non-comparative study, pregnant women were identified as having high levels of non-adherence, inadequate knowledge of asthma inhaler technique, and insufficient knowledge of asthma management strategies.[12] Further, less than 20% of women reported having an asthma action plan to assist them in the management of exacerbations during pregnancy.[12] The intervention itself was effective in improving skills and knowledge about asthma during pregnancy. A more recent prospective before-after study reported on the impact of the introduction of a nurse-led antenatal asthma management service on asthma related outcomes during pregnancy.[27] The introduction of this service was associated with a reduction in loss of control (RR 0.67; 95%CI 0.46-0.99), persistent uncontrolled asthma (RR 0.48; 95%CI

0.26-0.90), and asthma exacerbations (RR 0.69; 95%CI 0.33-1.42).[27] The prevalence of exacerbations reduced from 19.1% to 15% (p=0.48) following the intervention. The most robust evidence for the impact of antenatal asthma self-management education comes from a recent Australian randomised controlled trial. This involved randomisation of 60 women with asthma at less than 20 week's gestation to receive either usual care or a pharmacist-led asthma management intervention. The intervention consisted of multidisciplinary care, education and regular monthly monitoring throughout pregnancy and was associated with a subsequent reduction in asthma control questionnaire (ACQ) scores at 3 months (-0.22 95%CI: -0.54, 0.10) and 6 months (-0.60 95%CI -0.85, -0.36) compared to those receiving usual care.[42] Notably, no women in either group reported experiencing any exacerbations during the study, despite the noted differences in asthma control.

Awareness of the benefits of improved asthma control through regular self-monitoring of symptoms and self-management according to a written asthma action plan led to the trial of a telehealth based intervention in pregnant asthmatics.[43] In this study the use of a mobile smartphone based application, which utilised a handheld respiratory device to support women in regularly monitoring their asthma and provided advice on how to management a deterioration in symptoms, was effective in improving asthma control over a 6-month follow-up period.[43] The major benefit of such an approach was that it removed the necessity for face-to-face visits and removing such barriers to care, with data on asthma symptoms electronically communicated to treating healthcare professionals enabling intervention where necessary. Importantly, while improvements in asthma control were identified across these studies, there was no evidence of associated improvements in perinatal outcomes.

4.2. Individualisation of asthma treatments

In recent years there has been growing interest in the identification and examination of differing asthma phenotypes.[44] The identification of such phenotypes has offered promise for the potential identification of those more likely to respond to a particular treatment or management strategy. There exists a number of examples demonstrating the success of such an approach.

For example, the presence of airway eosinophilia (which is associated with an inflammatory phenotype) is associated with more favourable response to corticosteroid therapy,[45-47] and a greater risk of exacerbations when corticosteroids are withdrawn.[48] In contrast, administration of ICS to individuals with non-eosinophilic asthma has been associated with a significantly poorer response to treatment and an increased likelihood of poor response to inhaled corticosteroids. [45, 46]

Such findings have stimulated interest in the identification of airway inflammation and its use as a tool to better guide asthma treatments. This approach was applied in pregnancy in the Managing Asthma in Pregnancy (MAP) study, which utilised the fraction of exhaled nitric oxide (FENO) and asthma symptoms to guide treatment decisions.[49] The use of this novel non-invasive approach was associated with a substantial reduction in the prevalence (41% vs. 25%; p=0.011) and incidence (incidence rate ratio 0.50, 95% CI 0.33–0.76; p=0.001) of women experiencing exacerbations during pregnancy.[49] A reduction in neonatal hospitalisations was also observed (n=8 [8%] *vs* 18 [17%]; p=0.046), but the study was specifically powered to look at perinatal outcomes. This, however, is the focus of a larger ongoing study which will recruit a much larger number of women and focus on whether this approach leads to improvements in perinatal health outcomes.[50] This ongoing study will also include women who smoke, which will address an important limitation from the previous study as smokers were excluded. Given the high proportion of asthmatic women who also smoke during pregnancy (>20%),[26] examining efficacy of this intervention

among these women is important to guide clinical practice. Notably, use of FENO to guide asthma treatment is not a stand-alone approach and does not replace the need for appropriate asthma self-management education.

4.3. Additional considerations for asthma management in pregnancy

4.3.1. Optimal target for improving outcomes of asthmatic pregnancies

While significant focus lies on improving asthma control during pregnancy, how asthma control is evaluated and defined remains a significant challenge for clinical practice and in clinical trials. Tools such as the ACQ or asthma control test (ACT) are commonly utilised in the evaluation of asthma control at a specific point in time,[25, 51] but there is an absence of tools available for evaluating asthma exacerbations.[52, 53] Asthma exacerbations are rather commonly classified based on specific events, such as requirement for hospital admission, emergency department presentation, unscheduled doctor visits, or receipt of oral corticosteroid course. The concern lies in how well such events reflect asthma control throughout pregnancy.[54] For example, women with poor self-awareness may not even recognise that their asthma control is deteriorating and may therefore not seek additional help, while the opposite may be true for those with greater self-awareness who may seek help much earlier. Therefore, while the presence of an asthma exacerbation during pregnancy has been associated with increased risks of adverse perinatal outcomes, data are limited on the relative impact of asthma control evaluated independently of asthma exacerbations.[54] Exacerbations identified during pregnancy likely reflect a surrogate marker for uncontrolled asthma during pregnancy, but their relative predictive value in identifying women with persistently poorly controlled asthma during pregnancy may be altered by the characteristics

of the population being studied. The requirement for greater focus on asthma control comes from recent findings of a prospective cohort study undertaken among a socially disadvantaged population, where asthma control, but not exacerbations, were associated with adverse perinatal outcomes.[8] When directly assessed in the clinical setting, many women were identified as having persistent uncontrolled asthma which could be considered a current exacerbation, but they had a lack of self-awareness to identify the extent of their symptoms or had simply ignored them. Such observations raise the possibility that direct evaluation of asthma control may have greater validity in predicting subsequent pregnancy outcomes than just exacerbations reported alone, but this remains to be determined.

4.3.2. Timing of interventions in pregnancy

The delay between the actual beginning of pregnancy, i.e. the time that women find out that they are pregnant to the time at which they begin to receive antenatal care, represents a likely challenge for improving perinatal outcomes in asthmatic pregnancies. The reality is that insufficient data are available to determine which periods of pregnancy are critical for optimised asthma control to reduce the risk of adverse outcomes. There is the potential that adverse outcomes could differ according to uncontrolled asthma in early pregnancy versus later pregnancy, highlighting an important area for future research. Such evidence would help identify critical periods of pregnancy to intervene to improve health outcomes. Currently, intervention studies have included women up until 20 weeks' gestation.[42, 49] While this may still be beneficial in improving asthma control in the second half of pregnancy, a recent prospective cohort study identified that 50% of asthma exacerbations occurred in women prior to 20 weeks' gestation, [8] highlighting the potential importance of earlier intervention strategies.

One approach lies in targeting asthma interventions as soon as women identify that they are pregnant, which may occur following an early visit to their GP for confirmation of pregnancy or antenatal booking appointment in the hospital, but for many this may still not occur until later into the second trimester. The other approach lies in ensuring initiatives are in place to encourage optimal asthma management among women of childbearing potential, such that they enter pregnancy in the best possible position. With previous research identifying that less than 20% of women entered pregnancy with an established asthma action plan,[12] this represents a key objective for identifying improvements in pre-conception based initiatives.

5. Conclusion

Overall, pregnancy represents a significant opportunity to optimize asthma therapy and maximize lung function in order to reduce the risk of acute exacerbations and resultant adverse perinatal outcomes. However, despite knowledge of the harms associated with asthma during pregnancy little has been done to improve its management and reduce associated perinatal morbidity and mortality within the antenatal setting. This lack of progress is largely based on a lack of high-quality studies on the management of maternal asthma and where studies do exist, they typically focus on surrogate markers of maternal wellbeing, including asthma control and exacerbations. The assumption has been that improving maternal asthma control will in turn lead to improved perinatal health outcomes, but whether this is realistic is unclear and existing evidence does not support clear improvements in perinatal health outcomes associated with any maternal asthma management intervention.

In the absence of such data to support specific interventions, it is important that maternal asthma is recognised within the antenatal setting as a contributing factor towards adverse pregnancy outcomes. This means that optimising asthma control should be a high priority

within the antenatal setting, with women advised about the importance of good asthma control, managing asthma actively throughout pregnancy by utilising their asthma medications, and managing exacerbations in a timely and effective manner.

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579 **Table 1. Overview of medications used in the management of asthma during pregnancy[6, 55]**

Medication	Usual Dose	Safety Data in Pregnancy
Inhaled bronchodilators		
Short-acting bronchodilators		Reassuring human data
Salbutamol/albuterol	100-200 mcg when required	
Terbutaline	500-1500 mcg when required	
Long-acting bronchodilators¤		Limited experience; reassuring data available for salmeterol or eformoterol
Salmeterol	25-50 mcg twice daily	
Eformoterol	6-12 mcg twice daily	
Vilanterol	25 mcg once daily	
Inhaled corticosteroids		Reassuring human data; beclomethasone, budesonide, or fluticasone propionate preferred due to greater experience
Beclomethasone	Low: 100-200 mcg/day Medium: >200-400 mcg/day High: >400 mcg/day	
Budesonide	Low: 200-400 mcg/day Medium: >400-800 mcg/day High: >800 mcg/day	
Ciclesonide	Low: 80-160 mcg/day Medium: >160-320 mcg/day High:>320 mcg/day	
Fluticasone propionate	Low: 100-200 mcg/day Medium: >200-500 mcg/day High: >500 mcg/day	
Systemic corticosteroids		Use of systematic corticosteroids associated with increased risk of oral cleft and adverse pregnancy outcomes (e.g. pre-eclampsia, preterm birth, small-for-gestational age), but likely confounded by maternal asthma severity
Prednisolone	Exacerbation: 37.5-50 mg once daily for 5-10 days Maintenance: Variable dose according to response	
Leukotriene receptor antagonist		Limited experience; reassuring human data available
Montelukast	10 mg daily	
Zafirlukast	20 mg twice daily	
Other treatments		
Omalizumab	75-375 mg every 2-4 weeks (dose according to weight and serum total IgE level)	Limited experience; reassuring human data
Theophylline	400-600 mg/day (dose according to theophylline level)	Reassuring human data; limited role in practice due to monitoring requirements and associated risk of toxicity

¤ Some available individually and in combination with ICS; should not be used for monotherapy

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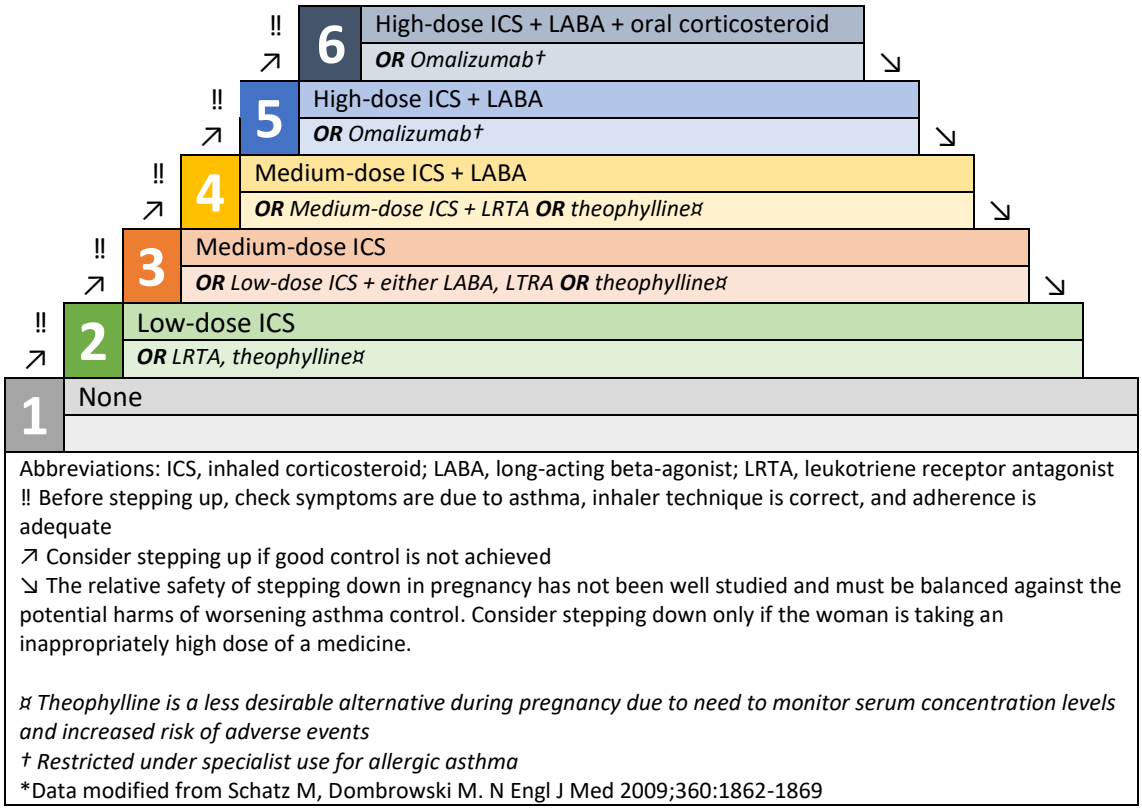
Figure 2. Stepped approach to adjusting asthma preventer therapy during pregnancy*



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LRTA, leukotriene receptor antagonist

‼ Before stepping up, check symptoms are due to asthma, inhaler technique is correct, and adherence is adequate

↗ Consider stepping up if good control is not achieved

↘ The relative safety of stepping down in pregnancy has not been well studied and must be balanced against the potential harms of worsening asthma control. Consider stepping down only if the woman is taking an inappropriately high dose of a medicine.

¤ Theophylline is a less desirable alternative during pregnancy due to need to monitor serum concentration levels and increased risk of adverse events

† Restricted under specialist use for allergic asthma

*Data modified from Schatz M, Dombrowski M. N Engl J Med 2009;360:1862-1869

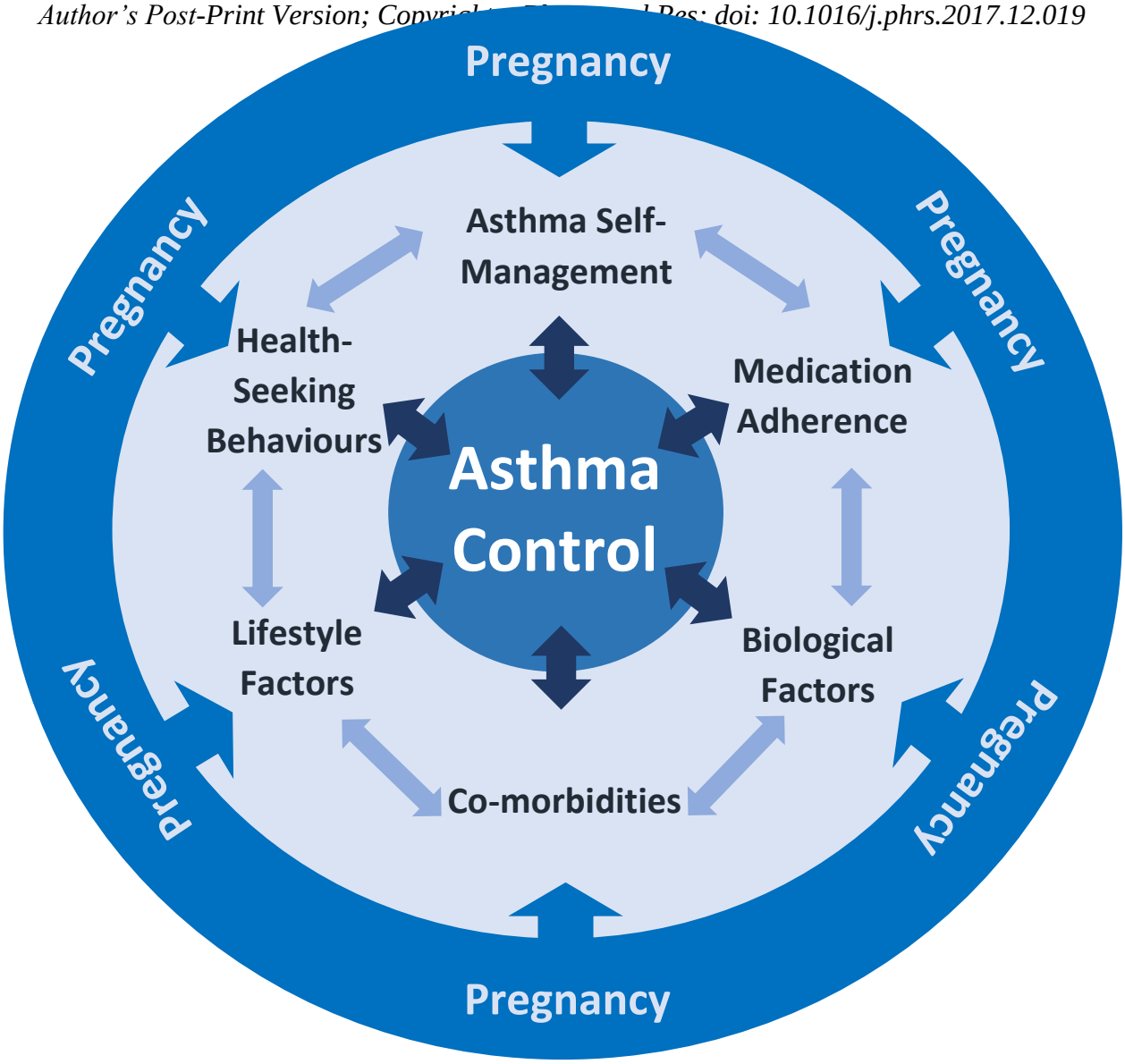


Figure 1. Interdependence of factors influencing asthma management with a focus on optimising asthma control during pregnancy