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Asthma management during pregnancy: how long before we can all breathe a little easier?

Journal of Asthma, 2015; 52(10):1020-1022

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This is an original manuscript / preprint of an article published by Taylor & Francis in Journal of Asthma, on 16 Sep 2015 available online: <http://dx.doi.org/10.3109/02770903.2015.1040494>

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19 March 2020

<http://hdl.handle.net/2440/123745>

Title Page

Long Title: Interventions for improving asthma management during pregnancy: how much longer before we can all breathe a little easier?

Short Title: Asthma Management in Pregnancy

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Keywords: antenatal care; asthma control; asthma exacerbations; perinatal care; medication adherence; fetus/drug effects; attitude to health

Word Count: 1957

Main Text

An urgent need exists for further investigation into the development of evidence-based approaches for improving asthma management during pregnancy and subsequent perinatal outcomes. Asthma is one of the most prevalent chronic medical conditions reported during pregnancy, with a prevalence between 8-13% worldwide [1]. Maternal asthma is associated with significant perinatal morbidity and mortality, with increased risk of low birth weight (RR 1.46; 95%CI 1.22-1.75), small-for-gestational age (RR 1.22; 1.14-1.31), preterm birth (RR 1.41; 1.22-1.61), pre-eclampsia (RR 1.54; 1.32-1.81), gestational diabetes (RR 1.39; 1.17-1.66) and Caesarean section (RR1.31; 1.22-1.39) [1, 2]. In Australia, asthma affects an estimated 12% (>37,000) pregnancies each year, with prevalence of asthma greatest (up to 16%) among the socially disadvantaged [3]. Using these figures and the risk of preterm birth associated with maternal asthma, conservative estimates would attribute maternal asthma to absolute increases of >1,200 preterm births each year, equating to one potentially preventable preterm birth every 7 hours. In the United States, for comparison, conservative estimates based on national statistics would be >18,000 preterm births each year, or one excess preterm birth approximately every 30 minutes due to maternal asthma. Despite such bleak statistics, a recent Cochrane review on interventions for managing asthma in pregnancy concluded that there was insufficient evidence of benefits and harms to be sure about the best way to manage asthma in pregnancy [4], highlighting the relative paucity of data upon which current clinical care is provided to pregnant asthmatics. Therefore, the aim of this commentary is to shine a light on current evidence, while highlighting key gaps in our current understanding and promote further research in this area.

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 can affect pregnancy outcomes. Existing recommendations are that asthma be managed during pregnancy in the same manner as a non-pregnant adult, including management of asthma medications [5]. This also applies to the assessment of asthma control and adjusting inhaled medications accordingly at regular intervals during pregnancy. Despite guidelines and awareness of the substantial adverse effects associated with asthma during pregnancy, little has been done to improve its management and reduce associated perinatal morbidity and mortality. Anecdotally, while a small number of women with very severe asthma receive monitoring during

pregnancy in the antenatal clinic with respiratory specialist support, treatment is often limited to women self-managing their asthma with support from their GP. Therefore, current asthma management appears to be focused on a reactive, not proactive, approach. This is highlighted through only 5-15% of asthmatic pregnant women involved in previous studies reporting having a current asthma action plan [6, 7].

In particular, pregnancy has a unique effect on decisions around asthma control and management. Despite clear guidelines recommending the continuation of asthma medications in pregnancy, it is not uncommon for women to cease their medications, with or without consultation with doctors [8]. Medication non-adherence has been previously demonstrated to be a key driver of worsening asthma during pregnancy [9]. These decisions may be driven by a perceived lack of need to continue their medications, a lack of support and guidance from health professionals regarding how to manage their asthma medications and/or concerns regarding the safety of asthma medications during pregnancy [10]. These concerns may not be unique to women themselves, as a previous survey demonstrated that in situations where asthma was well controlled, over 25% of family physicians would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy [11]. This is despite reassuring data on the safety of the majority of asthma medications during pregnancy, with the benefits of good asthma control greatly outweighing any potential risks associated with treatment [5]. As such, the uncertainty, concerns and variability in practice surrounding medication use and asthma control during pregnancy emphasises the fundamental need for multi-faceted approaches towards improving asthma management.

One of the first and largest RCTs to evaluate such non-pharmacological approaches was the Australian Managing Asthma in Pregnancy (MAP) study [12]. This study demonstrated that use of exhaled fraction of nitric oxide ($F_{E}NO$), as a measure of inflammation, to adjust asthma management during pregnancy, was associated with a significant 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 [12]. Further, there was also a reduction in neonatal hospitalisations (eight [8%] vs 18 [17%]; $p=0.046$), suggesting potential improvements in perinatal outcomes through improved asthma

control. The main limitation of this trial, however, was that only non-smokers were enrolled, as cigarette use inhibits exhaled NO production in asthmatics and therefore can significantly mask the interpretation of NO data. This restricts the generalisability of this approach given the high proportion of asthmatic women who also smoke during pregnancy (>20%) [3]. In addition, it has been suggested that the applicability of F_ENO to routine clinical settings may be further limited due to issues around clinical expertise, expense and accessibility [7]. Most important, use of FENO is not a stand-alone approach towards improving asthma management, and does not replace the need for appropriate asthma self-management education. In this study women were initially provided with asthma self-management skills including inhaler technique, knowledge, action plan, and adherence at their initial study visit. Ongoing monthly visits, however, were completed by blinded research assistants without additional respiratory training. Therefore, it is not possible to determine whether ongoing review and reinforcement of asthma self-management skills at later visits would have provided additional benefit.

This brings the focus towards asthma self-management education, which is seen by many as an approach that is portable and transferable across healthcare settings. In adults, previous studies have identified that the provision of asthma self-management education compared to usual care reduces asthma exacerbations [13]. Whether these interventions translate to the antenatal setting remains undetermined as uncertainty, concerns, and variability in practice surrounding medication use and asthma control during pregnancy are prevalent. Previous non-randomised studies have demonstrated the effectiveness of self-management education in improving skills and knowledge about asthma during pregnancy [6]. This service was built on successful adult programmes incorporating education, self-monitoring, regular review with optimisation of pharmacotherapy and a written plan for the management of unstable asthma [6]. Further, this study identified that the majority of women have poor asthma self-management skills and knowledge, regardless of the severity of their asthma [6].

Most recently, evidence in support of the provision of asthma self-management education during pregnancy is provided through another Australian RCT [7]. Participants with current asthma (N=60) were recruited up until 20 weeks gestation from the antenatal clinic and randomised to either standardised usual care or a pharmacist-led intervention consisting of multidisciplinary care, education

and regular monthly monitoring of asthma throughout pregnancy. The primary outcome was a change in Asthma Control Questionnaire (ACQ) scores at 3 and 6 months following randomisation. The difference between the groups, adjusting for baseline ACQ score, was -0.22 (95%CI: -0.54, 0.10) at 3 months and -0.60 (95% CI -0.85, -0.36) at 6 months [7]. While these findings of a reduction in ACQ score are very promising they raise the question of what the ideal end-point should be for studies relating to asthma management in pregnancy. While ACQ is recognised as a well validated tool for assessing asthma control and guiding asthma management, the reality is that it provides a snapshot of asthma control over the previous week, with no previous studies demonstrating how well this relates to asthma control across the entire pregnancy. While exacerbations are often the result of poor asthma control, despite significant improvements in asthma control between groups at the conclusion of the study by Lim et al., no women in either group reported experiencing any exacerbations during the study. In contrast, in the MAP study by Powell et al. no statistically significant differences in ACQ scores were evident between groups at the end of the study, despite the intervention group experiencing greater than a 50% reduction in the incidence of exacerbations across gestation [12]. This raises questions regarding the possibly subjective and variable manner in which exacerbations may be defined, given they often rely on individual awareness of symptoms and self-help seeking behaviours (e.g. unscheduled doctor or ED visit) [14]. Notably, however, Powell et al. identified a mean ACQ score of 2.03 (SD 0.76) during unscheduled doctor visits suggesting that pregnant women reporting an exacerbation were indeed experiencing poor asthma control. Arguments aside about whether asthma control, exacerbations, or a combination of both, represents the key study end-point, what appears clearer is that for studies targeting interventions towards improving asthma management during pregnancy, these end-points remain surrogates for resultant improvements perinatal outcomes. While exacerbations are strongly linked with adverse perinatal outcomes in previous observational studies [9, 15, 16], further adequately powered studies are urgently required to determine whether improvements in asthma control and reduction in exacerbations associated with specific interventions actually lead to the desired improvements in perinatal outcomes.

An additional challenge consistent across previous studies and current clinical practice relates to the timing in which asthmatic pregnancies are identified and then provided with an additional intervention. In existing studies, recruitment of pregnant women occurs up until 20 weeks gestation. Introducing interventions in mid-pregnancy could possibly be too late to optimise perinatal outcomes, with Lim et al. identifying that greater than 15% of women reported a moderate/severe exacerbation prior to study recruitment [7]. While optimised management in the pre-conceptual period is ideal, this is often unachievable. An ideal approach could be targeted asthma self-management education 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. Notably, this raises the urgent need to examine the impact of exacerbations occurring at different time points during gestation on perinatal outcomes. It is likely that clinical outcomes could differ according to the timing of exacerbation, with earlier exacerbations impacting on placental development, risk of spontaneous abortion and fetal growth, while later exacerbations could have a more significant impact on the risk of preterm birth.

Ultimately, pregnancy represents a significant opportunity to optimize therapy and maximize lung function in order to improve asthma control and reduce the risk of adverse perinatal outcomes. There remains an urgent need for additional studies evaluating interdisciplinary interventions towards improving asthma management in pregnancy, with a specific focus on improving perinatal outcomes. Ideally, such interventions should; (a) build on existing synergies between the primary health care and secondary/tertiary hospital settings, (b) be able to be introduced in any setting where pregnant women are cared for, which include hospitals, GP offices, and regional health services, and (c) be evaluated for not only their clinical effectiveness, but also their cost effectiveness, given limited healthcare funding. Evidence derived from such studies will go a long way towards providing compelling evidence in support of new policies for the care of pregnant asthmatic women and models of health service delivery.

In the absence of enhanced models of care to facilitate improvements in asthma management during pregnancy it is essential that antenatal care providers recognise that untreated asthma, poorly controlled asthma, or asthma exacerbations during pregnancy could lead to adverse perinatal outcomes. This

means that good asthma control should be a high priority. In short, efforts to reduce asthma-related risk in pregnancy are essential and involve giving preconception advice to women with asthma where possible, advising pregnant women about the importance of good asthma control, managing asthma actively throughout pregnancy and managing exacerbations in a timely and effective manner. Such efforts could have immediate and long-term benefits to women and their babies and help reduce the significant health burden associated with asthma during pregnancy.

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